National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immune Checkpoint Inhibitor-Related Toxicities

Version 1.2026 — October 23, 2025

NCCN Guidelines for Patients®

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

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NCCN Guidelines Panel Disclosures

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

See NCCN Categories of Evidence and Consensus.

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

Global Changes
- Guideline name changed from NCCN Guidelines for the Management of Immunotherapy-Related Toxicities to NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities
- Guideline content on CAR-T and Lymphocyte-engagers now published in a separate Guideline: NCCN Guidelines for the Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities
- References updated throughout the Guidelines.
- Myasthenia gravis changed to 'myasthenia gravis/myasthenia gravis-like syndrome' throughout the Guidelines.
- IVIG content modified to 'IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information' throughout the Guidelines.

Principles of Routine Monitoring for Immune Checkpoint Inhibitors

IMMUNO-2
- Fertility section added

Conditions-Signs and Symptoms

IMMUNO-3
- ENDO ~~Overt~~ hypothyroidism modified: Fatigue, lethargy, sensation of being cold, possible constipation, bradycardia. *Patient may be asymptomatic or exhibit minimal symptoms*

IMMUNO-4
- MUSCULO: Polymyalgia rheumatica (PMR) modified: PMR symptoms: *stiffness with inactivity*, fatigue and/or muscle and joint pain typically in shoulders and hips

IMMUNO-5
- OCULAR: Vision changes modified: Blurred/distorted vision, new floaters, itchy eyes, blind spots, change in color vision, *diplopia*, photophobia, tenderness/pain, eyelid swelling, and proptosis. Scleritis can cause a reddish purple discoloration of the eye. Uveitis can be associated with eye redness.

Infusion-Related Reactions

ICI_INF-1
- Management
  - Mild transient reaction (G1), 3rd bullet modified: Consider premedication with acetaminophen, ~~H2 blockers,~~ and *antihistamines (H1 and H2)* ~~diphenhydramine~~ with future infusions (Also Moderate [G2])

Dermatologic Toxicity

ICI_DERM-1
- Maculopapular rash
  - Management
    - ◊ Severe, 3rd bullet modified: Prednisone/IV methylprednisolone 0.5–1 mg/kg/day ~~(increase dose up to 2 mg/kg/day if no improvement)~~

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

ICI_DERM-2
- Pruritus
  - Assessment/Grading
    - 2nd bullet added: Consider testing for sources of pruritus including bullous pemphigoid antibodies, BUN/creatinine, hepatic function tests, thyroid function tests, and bile acids
  - Management
    - Moderate (G2) combined with Severe (G3)
- Footnote n added: Including topical products that have the following active ingredients: hydrocortisone 0.5% or 1%, diphenhydramine, pramoxine, camphor, menthol.

ICI_DERM-3
- Bullous dermatitis
  - Management, Severe (G3) OR Life-threatening (G4)
    - 3rd bullet added: If bullous pemphigoid confirmed, dupilumab is recommended as a steroid-sparing measure
    - 4th bullet modified: Consider *alternative steroid-sparing options such as* IVIG ~~(1 g/kg/day x 2 days with monthly cycle until clear)~~ as an adjunct to rituximab ~~or dupilumab~~
- Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)
  - Management
    - 1st bullet modified: ~~Permanently~~ Discontinue immunotherapy
    - 2nd bullet added: Evaluate entire medication list for alternative culprit drug such as an antibiotic or anticonvulsant
    - 5th bullet modified: Consider IVIG ~~(1 g/kg/day in divided doses per package insert for 3–4 days)~~

ICI_DERM-4
- Lichen planus and lichenoid diseases
  - Management
    - Moderate: 10%–30% BSA or not responsive to high-potency topical steroids
      - 5th bullet added: Consider referral to dermatology
    - Severe: >30% BSA
      - 4th bullet, 4th sub bullet added: Dupilumab
      - Bullet removed: Doxycycline and nicotinamide

ICI_DERM-5
- Psoriasis and psoriasiform diseases
  - Management
    - Mild: <10% BSA
      - 3rd bullet added: Consider transitioning to non-steroidal topical therapies such as tacrolimus 0.1% or calcipotriene 0.005% for long-term management in intertriginous areas or facial locations (Also Moderate and Severe)
      - Bullet removed: Topical vitamin D analogues (Also Moderate and Severe)

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

ICI_DERM-6
- Oral mucosa inflammation
  - Management, General, 1st bullet modified: Dietary modifications, *nutritional evaluation and supplementation*

Endocrine Toxicity

ICI_ENDO-1
- Hyperglycemia
  - Diagnosis/Workup
    - 4th bullet added: If fatigue or other endocrine irAEs, evaluate for hypophysitis/adrenal insufficiency (see ICI_ENDO-3)

ICI_ENDO-2
- Thyrotoxicosis recommendations moved here from ICI_ENDO-3

ICI_ENDO-3A
- Footnote t added: For pre-operative patients who had neoadjuvant therapy and cortisol status is unknown, consider a random cortisol. If less than 2 mcg/dL, treat. If between 2 mcg/dL and 5 mcg/dL, treat and refer to endocrinology.
- Footnote u added: In patients who have had chronic steroid exposure from their regimen or have questionable cortisol levels, send for cosyntropin stimulation in the outpatient setting.

Fatigue

ICI_FTG-1
- This page was revised extensively.

Gastrointestinal Toxicity

ICI_GI-1
- Footnote c added: 10-20% of patients will have normal endoscopic evaluation but positive biopsies for ICI gastritis. Haryal A, et al. Cancer 2023;129:367-375.

ICI_GI-2
- Diarrhea/Colitis, Mild (G1)
  - Assessment/Grading, 2nd bullet modified: ~~Based on institutional availability, Consider~~ Fecal *calprotectin* ± lactoferrin~~/calprotectin~~ (Also ICI_GI-3, ICI_GI-4)
  - Management, 6th bullet, 2nd sub bullet modified: If negative and no infection, continue G1 management and consider adding mesalamine and/or cholestyramine ~~as needed~~

ICI_GI-3
- Diarrhea/Colitis, Moderate (G2)
  - Management
    - 4th bullet, 1st sub bullet modified: If colonoscopy or flexible sigmoidoscopy shows significant ulceration, ~~or extensive~~ non-ulcerative inflammation, *or microscopic colitis on histology*, consider adding infliximab or vedolizumab (Also ICI_GI-4)
    - 6th bullet added: For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise (Also ICI_GI-4)

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

ICI_GI-4
- Diarrhea/Colitis, Severe (G3-4)
  - Footnote removed: Fecal transplantation may be considered for immunosuppressant-refractory colitis based on institutional availability and expertise.

ICI_GI-5
- Footnote ff added: Prednisone with maximum dose of 60 mg/day has been shown to be effective in autoimmune hepatitis. Mack CL, et al. Hepatology 2020;72:671-722. (Also ICI_GI-6A)

ICI_GI-6
- Elevated ALT/AST
  - Management
    - General (G3 or G4), 1st bullet modified: Monitor PT/INR *weekly or more often if clinically indicated based on liver tests and patient condition* ~~periodically~~
    - G3
      - 2nd bullet modified: Initiate prednisone/IV methylprednisolone *0.5*-1 mg/kg/day (Also G4)
        - 1st sub bullet modified: If no improvement after 1–2 days, consider adding mycophenolate mofetil *or tacrolimus* (Also G4)
        - 1st sub sub bullet modified: *If refractory to mycophenolate mofetil or tacrolimus, consider tocilizumab* or other steroid-sparing immunosuppressive therapy (Also G4)

ICI_GI-6A
- Footnote jj modified: Other steroid-sparing ~~immunosuppressive~~ therapy may include ATG, *or* azathioprine~~, tacrolimus, or tocilizumab~~. Response to these agents may be delayed and may require prolonged therapy ~~(≥1 week)~~ in the treatment of irAEs.
- Footnote ll added: A total bilirubin >2.5 mg/dL plus international normalized ratio (INR) >1.5, ascites, or encephalopathy. Hountondji L et al. Aliment Pharmacol Ther 2024;60:1561–1572.

ICI_GI-7
- Elevated alkaline phosphatase
  - Management
    - G2
      - 2nd bullet modified: *Initiate* ~~Start~~ prednisone 0.5–1 mg/kg/day
      - 3rd bullet modified: ~~Consider~~ Ursodiol 13–15 mg/kg/day
    - G3/G4
      - 2nd bullet modified: Monitor *PT/*INR *if there is a high suspicion for elevated bilirubin/AST/ALT*
      - 4th bullet added: Ursodiol 13–15 mg/kg/day
      - Bullet removed: Consider Ursodiol 13–15 mg/kg/day

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

ICI_GI-7A
- Footnote rr modified: Ursodiol is available *in capsules (200 mg, 300 mg, 400 mg) and tablets (250 mg, 500 mg)* ~~as 150 mg and 300 mg capsules and can be administered as a single daily dose.~~ Split dosing (BID or TID) *with food should* ~~can~~ be considered *to enhance absorption and minimize GI side effects* ~~if patient experiences side effects such as diarrhea~~.
- Footnote ss modified: Other steroid-sparing immunosuppressive therapy may include ATG, azathioprine, tacrolimus, or tocilizumab. Response to these agents may be delayed and may require prolonged therapy ~~(≥1 week)~~ in the treatment of irAEs.

ICI_GI-8
- 1st column modified: Elevation in ~~amylase/~~lipase (asymptomatic)
  - Assessment/Grading
    - Mild modified: Mild ~~≤3 x ULN amylase and/or~~ ≤3 x ULN lipase
    - Moderate or Severe modified: Moderate ~~>3–5 x ULN amylase and/or~~ >3–5 x ULN lipase or Severe ~~>5 x ULN amylase and/or~~ >5 x ULN lipase
  - Management
    - Mild, 3rd bullet modified: Consider other causes for elevated ~~amylase/~~lipase
    - Moderate or Severe
      - 2nd bullet, 2nd sub bullet modified: If persistent moderate to severe ~~amylase and/or~~ lipase elevation, abdominal CT with contrast or MRCP
      - 3rd bullet modified: Consider other causes for elevated ~~amylase/~~lipase
- Footnote vv modified: Routine ~~amylase/~~lipase assessments do not have to be performed outside of clinical suspicion of possible pancreatitis. See Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

ICI_GI-9
- Acute pancreatitis
  - Assessment/Grading
    - 5th bullet added: Assess for IgG4; If positive, manage as autoimmune pancreatitis
  - Management
    - Mild (G2), 4th bullet modified: Manage as per elevation in ~~amylase/~~lipase (asymptomatic) (ICI_GI-8)
    - Moderate (G3), Bullet removed: Consider prednisone/IV methylprednisolone 0.5–1 mg/kg/day only if no improvement with hydration and pain control (Also Severe [G4])
    - Severe (G4), 2nd bullet added: Inpatient care
- Footnote yy modified: Asymptomatic ~~amylase/~~lipase elevation OR radiologic features on CT or clinical findings concerning for pancreatitis. The decision to hold immunotherapy is based on clinical suspicion. If ~~amylase/~~lipase >3 x ULN or CT findings are prominent, holding immunotherapy is recommended.
- Footnote zz modified: Symptomatic pain or vomiting AND any ~~amylase/~~lipase elevation or CT findings suggesting pancreatitis.
- Footnotes removed:
  - The data supporting the use of steroids for the treatment of pancreatitis are limited.
  - Treat until symptoms improve to grade ≤1, then taper over 4–6 weeks.

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

Hematologic Toxicity

ICI_HEM-1

- 1st column modified: Unexplained drop in hemoglobin (Hb) ~~and/or platelets in the absence of bleeding source~~
- Assessment
  - 1st bullet modified: *Evaluate for common causes of anemia such as bleeding (e.g. fecal occult blood test) and iron, B12, and folate deficiencies* ~~Rule out non-ICI–related causes (eg, other medications)~~
  - 5th bullet modified: *Direct antiglobulin test (DAT) and* cold agglutinin *study if immune hemolysis is suspected*
  - Bullet removed: Direct antiglobulin test (DAT)
- Footnote e modified: Findings may overlap with the traditional HLH diagnostic criteria (ie, HLH2004/HLH1994). Clinical findings may include: unexplained fever *and* hepatosplenomegaly ~~sequelae of low counts, hypofibrinogenemia, elevated ferritin (≥500 ng/mL), and transaminitis~~. Laboratory findings may include: *low counts, hypofibrinogenemia, elevated ferritin (≥500 ng/mL)*, elevated soluble IL-2 receptor levels (based on CD25), absent/low natural killer (NK) cell activity according to local laboratory reference, ~~and~~ hypertriglyceridemia *and transaminitis*. Histopathologic findings include: accumulation of lymphocytes/macrophages and hemophagocytosis; these may be identified via tissue biopsy, such as bone marrow, liver, or other tissues with suspected involvement (Henter JI, et al. Pediatr Blood Cancer 2007;48:124-131). (Also ICI_HEM-4)

ICI_HEM-2

- Hemolytic anemia
  - Assessment
    - ◊ 3rd bullet added: Evaluate for and rule out other non-ICI– related etiologies of hemolytic anemia
    - ◊ 1st sub bullet added: Examples include viruses, bacteria, use of certain drugs [examples include dapsone], methemoglobinemia, bone marrow failure syndrome, or insect or reptile bites
    - ◊ Bullet removed: Glucose-6-phosphate dehydrogenase (G6PD)
  - Management, Grade 4: Hemolysis and life-threatening consequences requiring urgent intervention
    - ◊ 5th bullet, 1st sub bullet modified: If no response to steroids and rituximab, consider IVIG, tacrolimus, cyclophosphamide, mycophenolate mofetil, *or* cyclosporine~~, ATG, or infliximab~~

ICI_HEM-2A

- Footnote removed: Hemolytic anemia can have non-ICI–related causes such as viruses or bacteria, insect or reptile bites, use of certain drugs (eg, dapsone), methemoglobinemia, or bone marrow failure syndrome.

ICI_HEM-3

- Aplastic anemia
  - Assessment, 4th bullet added: Evaluate for and rule out other non-ICI–related etiologies of aplastic anemia
    - ◊ 1st sub bullet added: Examples include radiation exposure, certain toxins, viruses, infections, or prior treatments
  - Management, Severe or Very severe
    - ◊ 4th bullet, 1st sub bullet modified: Consider IVIG, cyclosporine, ATG, mycophenolate mofetil, ~~and~~ *or* tacrolimus
- Footnote removed: Aplastic anemia can have other causes such as radiation exposure, certain toxins, viruses, infections, or prior treatments.

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

ICI_HEM-4
- HLH-like syndrome
  - Assessment, 4th bullet added: Consider natural killer (NK) cell activity assessment per institutional guidelines

ICI_HEM-5
- Thrombocytopenia
  - Assessment
    - 4th bullet added: PT/INR, partial thromboplastin time (PTT), fibrinogen
    - Bullet removed: DAT
    - 5th bullet added: Abdominal ultrasound
    - 8th bullet modified: *Evaluate for and* rule out *other non-ICI–related etiologies of thrombocytopenia*
      - 1st sub bullet modified: *Examples include* medication-related causes, *infection, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and HLH*

Musculoskeletal Toxicity

ICI_MS-1
- Inflammatory arthritis
  - Assessment/Grading
    - 4th bullet modified: Consider joint ultrasound, or joint MRI with *or without* contrast if diagnosis of synovitis is unclear
  - Management
    - Moderate, 3rd bullet, 2nd sub bullet: If unable to taper prednisone from 30 mg/day after 1 week, consider initiating csDMARD, ~~tumor necrosis factor (TNF) inhibitors,~~ IL-6 inhibitors (tocilizumab or sarilumab), *or tumor necrosis factor (TNF) inhibitors*
    - Severe, 3rd bullet, 1st sub bullet: If unable to taper after 1 week, consider initiating csDMARD, ~~TNF inhibitors,~~ or IL-6 inhibitors (tocilizumab or sarilumab) *or TNF inhibitors*
  - 5th column modified: Monitor with serial rheumatologic examinations ± ESR, CRP every 4–*8* ~~6~~ weeks after treatment

ICI_MS-1A
- Footnote b added: ICI IA can be seen with PMR-like manifestations.
- Footnote r added: In inflammatory arthropathies that have symptoms suggestive of psoriatic arthritis or spondyloarthropathies, consider agents that are approved for these indications such as apremilast, IL-17, IL-12, or IL-23 inhibitors.

ICI_MS-2
- Page moved from ICI_MS-3
- Footnote v added: ICI PMR can be seen with peripheral arthritis.

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

ICI_MS-3
- 1st column modified: Myositis (proximal muscle weakness, neck flexor weakness, *dysphagia,* with or without myalgias)
- Management
  - Severe or Life-threatening
    - 1st bullet modified: Hold immunotherapy; consider *permanent discontinuation in* ~~discontinuing for~~ select patients
    - 4th bullet modified: Consider IV methylprednisolone 500 mg to 1 g/day x 3 days followed by prednisone 1 mg/kg/day. After 4 weeks, taper prednisone by 10 mg~~/month~~ *every two weeks to 0.5 mg/kg/day and then 10 mg/month as clinical status allows.*
    - 5th bullet modified: *If significant dysphagia, life-threatening situations, or refractory to steroids with minimal improvement after 1 week,* consider IVIG ~~(2 g/kg administered in divided doses per package insert)~~, *methotrexate*, mycophenolate mofetil, or rituximab ~~for significant dysphagia, life-threatening situations, or cases refractory to steroids~~

ICI_MS-3A
- Footnote aa added: Myocarditis symptoms are nonspecific (eg, chest pain, dyspnea, fatigue, palpitations [arrhythmia: heart block or ventricular ectopic beats], syncope, generalized weakness) and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis/myasthenia gravis-like syndrome (3 M's), and more common with combination therapy. In most fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.
- Footnote ll added: Methotrexate 15-25 mg weekly by oral or subcutaneous route.

Nervous System Toxicity

ICI_NEURO-1
- Myasthenia gravis*/myasthenia gravis-like syndrome*
  - Assessment/Grading
    - 1st bullet: Evaluate for concomitant irAEs myocarditis (ICI_CARDIO-1) and myositis (ICI_MS-3) as myasthenia gravis*/myasthenia gravis-like syndrome* can exist as an overlap syndrome, moved here from 4th bullet
  - Management
    - Moderate (G2)
      - 4th bullet modified: Pyridostigmine 30 mg *3 times a day* ~~TID~~ and gradually increase to maximum of 120 mg orally 4 times a day as tolerated and based on symptoms
- Footnote b added: Myocarditis symptoms are nonspecific (eg, chest pain, dyspnea, fatigue, palpitations [arrhythmia: heart block or ventricular ectopic beats], syncope, generalized weakness) and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis/myasthenia gravis-like syndrome (3 M's), and more common with combination therapy. In most fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.

ICI_NEURO-4
- Encephalitis
  - Assessment
    - 5th bullet modified: Electroencephalogram (EEG) to evaluate for *non-convulsive* ~~subclinical~~ seizure

ICI_NEURO-5
- Demyelinating Disease
  - Management
    - 5th bullet added: For management of optic neuritis, see ICI_OCUL-3

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

Ocular Toxicity
- This section has been extensively revised and expanded.

Pulmonary Toxicity

ICI_PULM-1
- Moderate (G2) pneumonitis
  - 4th bullet, 1st sub bullet: Consider *early* bronchoscopy with BAL (send for institutional immunocompromised panel) and consider transbronchial lung biopsy if clinically feasible to *evaluate* for ~~rule out~~ progressive malignancy, fungal infections, or steroid responsive interstitial lung disease (ILD)
  - 6th bullet, 1st sub bullet: Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for *steroid-dependent* ~~recurrent~~ pneumonitis at the time of steroid tapering

ICI_PULM-2
- Severe (G3–4) pneumonitis
  - 1st bullet modified: ~~Discontinue~~ *Hold* immunotherapy
    - ◊ 8th bullet
      - – 1st sub bullet, 2nd sub sub bullet: Tocilizumab, moved here from Other Recommended
      - – 2nd sub bullet, 1st sub sub bullet: Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service, moved here from Preferred
        - ▪ 1st sub sub sub bullet added: Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for steroid-dependent pneumonitis at the time of steroid tapering

ICI_PULM-2A
- Footnote j modified: Viral pathogen assessment should include *influenza*, COVID-19, *and respiratory syncytial virus (RSV).*

Principles Of Immunosuppression For Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

IMMUNO-A 1 OF 3
- Principles of Steroid Use in the Management of irAEs
  - 5th bullet, 2nd sub bullet added: Patients who are initiated on longer steroid tapers should have close follow-up with oncologist or co-managing disease-specific subspecialist team to monitor for side effects of steroid use, and to evaluate any need for modifying immunosuppressant regimen as appropriate based on clinical improvement of irAE.

IMMUNO-A 3 OF 3
- Header modified: Principles of Immune Checkpoint Blockade in Patients with Pre-Existing Autoimmune*/Viral* Conditions or Organ Transplant Recipients
- 1st bullet modified: Patients with a history of HIV or viral hepatitis may be candidates for immunotherapy. *See the NCCN Guidelines for Cancer in People with HIV.*

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities from Version 1.2025 of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities include:

Principles Of Immunotherapy Patient Education

IMMUNO-B 2 OF 3
- Health Care Provider (HCP) Information
  - Toxicity Management
    - Severe AEs, 5th bullet added: Ensure appropriately timed follow-up visits with oncologist or co-managing disease-specific subspecialist team for patients who required hospitalization for severe AEs. Close monitoring is encouraged as these patients are likely to have been started on new medications such as immunosuppressive agents and hormone replacement therapy that may require further adjustment or re-evaluation after hospitalization.

Principles Of Immunotherapy Rechallenge

IMMUNO-C 1 OF 3
- Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold
  - Eye:
    - 1st bullet modified: ~~Grade 2–4 irAE:~~ Hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology ~~on resolution to ≤ grade 1~~.

IMMUNO-C 2 OF 3
- Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold
  - Lung:
    - 2nd bullet modified: Grade 2*/3*: *Consider resuming* ~~Resume~~ once pneumonitis has resolved to ≤ grade 1 and patient is off steroids. ~~Resume once pneumonitis has resolved to ≤ grade 1 and patient is on a steroid dose of ≤10 mg/day of prednisone.~~
  - Musculoskeletal:
    - 2nd bullet modified: Severe *or life-threatening myositis* (with or without myocarditis): *Consider* permanent discontinuation *in select patients* ~~is recommended~~ due to high risk of morbidity/mortality.

IMMUNO-C 3 OF 3
- Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold
  - Pancreas:
    - 1st bullet modified: Symptomatic grade ≤3 pancreatitis: Consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in ~~amylase/~~lipase. Consider consultation with relevant pancreatic specialist regarding resumption.
    - 2nd bullet modified: Permanent discontinuation is warranted for severe (grade 4) pancreatitis *and other related complications (eg. abscess, fistula)*
  - Skin:
    - 2nd bullet modified: ~~Permanent~~ Discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Patient and relevant family history of any autoimmune/ organ-specific disease, endocrinopathy, or infectious disease (ID) • Neurologic examination • Bowel habits (typical frequency/consistency) • ID screening (human immunodeficiency virus [HIV]; hepatitis A, B, C) as indicated	Clinical examination at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General blood work • Complete blood count (CBC) (with differential if indicated) • Comprehensive metabolic panel (CMP)	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Consider dermatology referral. Monitor affected skin and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (FT4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	ICI_ENDO-2

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related AEs (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B). For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.

[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

Continued

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

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Pituitary/Adrenal (ICI_ENDO-3) • Consider serum cortisol (morning preferred) and thyroid function as above	Consider repeating every 4–6 weeks during immunotherapy (immuno-oncology [IO]-only regimens[c]), then follow-up every 12 weeks as indicated	Morning serum cortisol, adrenocorticotropic hormone (ACTH), TSH, FT4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol (premenopausal individuals), and cosyntropin stimulation test only as indicated
Fertility • Advise on family planning and refer to fertility preservation specialists if desired		
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for patients who are high risk (eg, interstitial lung disease [ILD] on imaging, chronic obstructive pulmonary disease [COPD], previous suspected treatment-related lung toxicity) • In the absence of prior imaging, consider a chest x-ray	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes
Cardiovascular (ICI_CARDIO-1) • Consider baseline electrocardiogram (ECG) • Consider high-sensitivity troponin and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms[d]	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine kinase (CK)

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of irAEs. See Principles of Immunotherapy Patient Education (IMMUNO-B). For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.
[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.
[c] For regimens that require steroid premedication, routine surveillance is not recommended.
[d] For individuals with a high-risk profile (eg, receiving immune checkpoint inhibitor [ICI] combination therapy regimens, including those with LAG-3), consider checking high-sensitivity troponin every cycle for the first 3 cycles (which corresponds with the median time to onset of myocarditis), and then every 3 months.

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

CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
CARDIO: Myocarditis	Chest pain, dyspnea, fatigue, palpitations (arrhythmia: heart block or ventricular ectopic beats), syncope, generalized weakness. This AE may occur in conjunction with myositis and/or myasthenia gravis; these entities must be ruled out.
DERM: Bullous dermatitis	Inflammation of the skin and the presence of bullae, which are filled with fluid. The most common immune-related bullous dermatitis is bullous pemphigoid. May be intense or widespread; intermittent; skin changes from scratching (eg, edema, excoriations, lichenification, oozing/crusts); limiting instrumental activities of daily living (iADLs).
DERM: Maculopapular rash (morbilliform rash)	Macules (flat) and papules (elevated)
DERM: Pruritus	Itching sensation, with or without rash
DERM: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% body surface area (BSA), respectively.
DERM: Lichen planus	Violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, significant pruritus. Erosions and striae (white lines intersecting) in the oral and vulvar mucosa.
DERM: Psoriasis and psoriasiform disease	Thick red scaly plaques, accentuated on extensor surfaces, scalp, umbilicus, postauricular surfaces
DERM: Oral mucosa inflammation	Irritated gums and/or oropharynx, red/white lesions and/or ulcers, lichen planus, mucositis
DERM: Dry mouth (Sicca syndrome)	Dry mouth (may cause difficulty with speaking, eating, swallowing, and/or staying asleep), oral sensitivity, dysarthria, dysphagia, dysgeusia, dental caries/erosion with prolonged salivary hypofunction, dry eye, lack of lubrication
DERM: Oral dysesthesia	Pain most often described as "burning" in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings
ENDO: Hyperglycemia-related diabetic ketoacidosis (DKA)	Excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, fruity odor on the breath
ENDO: Hypothyroidism	Fatigue, lethargy, sensation of being cold, possible constipation, bradycardia. Patient may be asymptomatic or exhibit minimal symptoms
ENDO: Thyrotoxicosis due to thyroiditis	Most patients with thyrotoxicosis due to thyroiditis have minimal, if any symptoms. If symptoms do arise, may include (uncommonly) tachycardia, tremor, anxiety, enlarged and tender thyroid gland (rarely).
ENDO: Hypophysitis	Acute onset headache, photophobia, nausea/emesis, fatigue, muscle weakness; may have low blood pressure
ENDO: Primary adrenal insufficiency	High ACTH with low morning cortisol, abnormal cosyntropin stimulation test. This is a rare diagnosis not usually associated with checkpoint immunotherapy.
ENDO: Central hypothyroidism	Symptoms of overt hypothyroidism (fatigue, bradycardia, lethargy, sensation of being cold, possible constipation) plus symptoms of central adrenal insufficiency (nausea/emesis, not feeling well, generalized malaise)

Continued

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

CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
GI: Esophagitis/Gastritis/ Duodenitis	Nausea, vomiting, dyspepsia, abdominal pain, anorexia
GI: Diarrhea/Colitis	Watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of gastrointestinal (GI) bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
GI: Transaminitis	Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
GI: Cholestasis	Elevated alkaline phosphatase (predominant) with or without bilirubin/AST/ALT elevation
GI: Pancreatitis	Acute pancreatitis: epigastric pain, nausea, possible vomiting Chronic pancreatitis: chronic abdominal pain, deficiency in pancreatic enzyme production with possible malabsorption
HEM: Hemolytic anemia	Asthenia, pallor, dark-colored urine, jaundice
HEM: Aplastic anemia	Symptoms secondary to anemia, thrombocytopenia, neutropenia, and infection (dyspnea, fatigue, tachycardia, ecchymosis, pallor, fever)
HEM: Hemophagocytic lymphohistiocytosis (HLH)-like syndrome	Unexplained fever, hepatosplenomegaly, sequelae of low counts, hypofibrinogenemia, elevated ferritin, transaminitis
MUSCULO: Inflammatory arthritis	Joint pain, joint swelling; inflammatory symptoms: stiffness after inactivity, improvement with activity
MUSCULO: Myositis	Myositis is characterized by inflammation and/or weakness involving the skeletal muscles. This adverse AE may occur in conjunction with myocarditis and/or myasthenia gravis; these entities must be ruled out. Common presenting symptoms may include muscle weakness, elevated CK, elevated transaminases, and myalgias.
MUSCULO: Polymyalgia rheumatica (PMR)	PMR symptoms: stiffness with inactivity, fatigue and/or muscle and joint pain typically in shoulders and hips
MUSCULO: Giant cell arteritis (GCA)	Visual symptoms, headache, scalp tenderness, jaw claudication
NEURO: Aseptic meningitis	Headache, photophobia, and neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
NEURO: Encephalitis	Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality
NEURO: Guillain-Barré syndrome (GBS)	Progressive, most often symmetrical, ascending muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in lower back and thighs.

Continued

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

CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
NEURO: Myasthenia gravis/myasthenia gravis-like syndrome	Progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (ie, ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis and myocarditis, which must be ruled out. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller Fisher variant of GBS has overlapping symptoms (ophthalmoplegia and ascending weakness).
NEURO: Peripheral neuropathy	Asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless paresthesias or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit. GI tract paresis due to myenteric neuritis is a rare toxicity associated with immune checkpoint inhibitor (ICI) therapy. The presentation may be fulminant with profound ileus.
NEURO: ADEM (acute demyelinating encephalomyelitis)	Headache, confusion, seizures, depressed level of consciousness, speech abnormality, focal weakness, sensory change (numbness or tingling), ataxia/loss of balance, or vision loss.
NEURO: Optic neuritis	Vision loss, eye pain, decreased visual acuity, visual field loss, dyschromatopsia, relative afferent pupillary defect, optic disc edema.
NEURO: Transverse myelitis	Acute or subacute weakness or sensory changes bilaterally, often with bowel/bladder changes and spinal level to pinprick, hyperreflexia, positive Babinski.
OCULAR: Vision changes	Blurred/distorted vision, new floaters, itchy eyes, blind spots, change in color vision, diplopia, photophobia, tenderness/pain, eyelid swelling, and proptosis. Scleritis can cause a reddish purple discoloration of the eye. Uveitis can be associated with eye redness.
PULM: Pneumonitis	Dry cough, shortness of breath, fever, chest pain
RENAL: Acute kidney injury (AKI)	Elevation of creatinine/blood urea nitrogen (BUN), inability to maintain acid/base or electrolyte balance, and urine output change (usually decreased)

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

ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT
Infusion-related reactions[a] →	• Physical exam • Vital signs • Pulse oximetry • ECG (if chest pain or sustained tachycardia)	Mild transient reaction (G1) →	• Hold until symptoms resolve, then resume infusion as tolerated • Intervention not indicated • Consider premedication with acetaminophen, and antihistamines (H1 and H2) with future infusions
		Moderate (G2)[b] →	• Treat per institutional guidelines • Consider holding or slowing the rate of infusion to half rate • Continue immunotherapy • Consider premedication with acetaminophen and antihistamines (H1 and H2) with future infusions ‣ Consider corticosteroids (steroids) for patients who previously experienced an infusion reaction; use of steroid premedication may be permitted in these situations
		Severe (G3–4)[c] →	• Treat per institutional guidelines • Discontinue offending immunotherapy; consider alternate agents in therapeutic class[d]

[a] Symptoms include: Fever/chills/rigors, back pain, urticaria/pruritus, angioedema, flushing/headache, hypertension, hypotension, shortness of breath, cough/wheezing, hypoxemia, dizziness/syncope, sweating, and arthralgia/myalgia. Refer to prescribing information for each individual immunotherapy agent for recommendations for premedication to prevent infusion reactions.

[b] Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤24 hours.

[c] Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement. Hospitalization indicated; life-threatening consequences; urgent intervention.

[d] If infusion reactions that are resistant to standard therapy occur in patients receiving programmed death ligand 1 (PD-L1) inhibitors, consider switching to a programmed cell death protein 1 (PD-1) inhibitor for subsequent treatments. There are no data to guide the use of alternate ICIs.

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

CARDIOVASCULAR ADVERSE EVENT(S)	SYMPTOMS/SIGNS	ASSESSMENT/GRADING		MANAGEMENT[f]
Suspected myocarditis/ Pericarditis/ Large vessel vasculitis[a] →	• Ventricular arrhythmias/ tachycardia • Conduction abnormalities/heart block • Heart failure • Cardiogenic shock • Pericardial effusion • Differential ‣ Myocardial infarction/ acute coronary syndrome ‣ Pulmonary embolism (PE); malignant involvement ‣ Other etiologies: viral, post-vaccination, other cardiotoxic medications →	• Immediate cardiology consultation (preferably cardio-oncology) • ECG (compare to baseline for any suspected cardiovascular AE) • Telemetry monitoring (inpatient)/topical patch monitoring (outpatient) • Echocardiogram (if possible with left ventricular [LV] strain measurement) • Cardiac biomarkers (troponin I or T, BNP, or NT-proBNP[b]) • Evaluate for concomitant immune-related AEs (irAEs), myasthenia gravis/myasthenia gravis-like syndrome[c] (ICI_NEURO-1), and myositis (ICI_MS-3), which can exist as an overlap syndrome with myocarditis ‣ Non-cardiac biomarkers[d] including CK, aldolase, and acetylcholine receptor (AchR) antibodies • Cardiac MRI with and without contrast (if possible)[e] • Consider cardiac catheterization and/or myocardial biopsy as clinically indicated • Consider viral titers	Myocarditis →	• Discontinue immunotherapy[g] • Management is tailored to response and acuity of presentation • High-dose steroids such as IV methylprednisolone 1 g/day for 3–5 days ‣ If responding and stable, switch to oral prednisone (1 mg/kg/day), then taper slowly over 6–12 weeks based on clinical response and improvement of biomarkers • If no improvement within 24–48 hours on steroids, initiate additional immunosuppression (listed in alphabetical order): ‣ Abatacept ‣ Alemtuzumab[h] ‣ Antithymocyte globulin (ATG) ‣ Infliximab[h] (use with extreme caution in patients with reduced LV ejection fraction [LVEF]) ‣ Intravenous immunoglobulin (Ig) (IVIG)[i] ‣ Methotrexate ‣ Mycophenolate mofetil[j] ‣ Plasmapheresis • Abatacept with ruxolitinib has been used in concomitant myositis and myocarditis[k] • Intensive care unit (ICU)-level monitoring • Temporary or permanent pacing as required
			Pericarditis/ Pericardial effusion →	• Consider myocarditis as a contributor • If myocarditis not present, manage as per usual recommendations[l]

Footnotes on ICI_CARDIO-1A

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

FOOTNOTES

[a] Myocarditis symptoms are nonspecific (eg, chest pain, dyspnea, fatigue, palpitations [arrhythmia: heart block or ventricular ectopic beats], syncope, generalized weakness) and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis/myasthenia gravis-like syndrome (3 M's), and more common with combination therapy. In most fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.
[b] Consider high-sensitivity troponin and NT-proBNP at baseline (for identifying those at increased risk) and serially during treatment to detect abnormal blood biomarkers that may precede symptomatic myocarditis induced by ICI.
[c] This can also be associated with thymoma.
[d] Consider ESR, CRP, or other inflammatory markers.
[e] Use of multiparameter tissue characterization by MRI, including T1 and T2 mapping and application of modified Lake Louise Criteria, provides important diagnostic value for myocarditis. If cardiac MRI is negative or myocarditis is highly suspected, consider endomyocardial biopsy.
[f] Principles of Immunosuppression (IMMUNO-A).
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] Perform a tuberculosis [TB] blood test (eg, T-Spot/QuantiFERON-TB Gold) (depending on facility) and hepatitis testing at time of suspected toxicity to facilitate administration.
[i] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[j] Mycophenolate mofetil treatment (0.5–1 g every 12 h).
[k] Salem JE, et al. Cancer Discov 2023;13:1100-1115.
[l] Adler Y, et al. Eur Heart J 2015;36:2921-2964.

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

DERMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[f]
Maculopapular rash[a] →	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases • Consider biopsy if unusual features • Eosinophil count, peripheral blood smear, and liver function tests (LFTs)[b]	Mild (G1)[c] →	• Continue immunotherapy • Topical emollient and moderate potency steroids[g] to affected areas • Consider trial of oral antihistamine for symptomatic relief of pruritus
		Moderate (G2)[d] →	• Continue immunotherapy • Topical emollient and moderate- to high-potency steroids[g] to affected areas • Consider trial of oral antihistamine for symptomatic relief of pruritus • If unresponsive to topical within 1–2 weeks, consider prednisone 0.5 mg/kg/day • Consider dermatology consultation
		Severe (G3)[e] →	• Hold immunotherapy[h] • Treatment with high-potency topical steroids[g] to affected areas • Prednisone/IV methylprednisolone 0.5–1 mg/kg/day[i] • Urgent dermatology consultation, consider biopsy • Consider inpatient care

[a] Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and may be associated with pruritus.

[b] These features can be used to assist with the diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome. This syndrome is typically characterized by a maculopapular rash that involves the face and ears and typically presents with swelling of the face and hands within 2–8 weeks after drug exposure. Note that certain classes of high-risk medications initiated in the prior few weeks may also cause maculopapular rash, including antiepileptic drugs: carbamazepine, phenytoin, lamotrigine, phenobarbital; antihyperuricemics: allopurinol, febuxostat; sulfonamides and sulphones: trimethoprim sulfamethoxazole, sulfasalazine, dapsone; and other antibiotics: vancomycin, minocycline, other beta-lactams. Kardaun SH, et al. Br J Dermatol 2013;169:1071-1080.

[c] Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness).

[d] Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting iADLs.

[e] Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care activities of daily living (ADLs).

[f] Principles of Immunosuppression (IMMUNO-A).

[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).

[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).

[i] Treat until symptoms improve to grade ≤1, then taper over 4–6 weeks.

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

DERMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[f]
Pruritus[j] →	• Total body skin exam, including mucosa • Consider testing for sources of pruritus including bullous pemphigoid antibodies, BUN/creatinine, hepatic function tests, thyroid function tests, and bile acids • Assess for history of prior inflammatory dermatologic diseases	General (G1, G2, or G3) →	• Oral antihistamines • Whole body moisturization with non-fragranced moisturizer
		Mild (G1)[k] →	• Continue immunotherapy • Treatment with moderate-potency topical steroids[g] to affected areas for localized pruritus • Consider over-the-counter topical anesthetic/anti-itch creams[n]
		Moderate (G2)[l] /Severe (G3)[m] →	• Hold immunotherapy[h] • Prednisone/IV methylprednisolone 0.5–1 mg/kg/day[i] • Consider gabapentinoids (gabapentin, pregabalin) ‣ If no response in 1 month, consider dupilumab, omalizumab, or narrow-band ultraviolet B (UVB) phototherapy • Urgent dermatology consultation

[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Treat until symptoms improve to grade ≤1, then taper over 4–6 weeks.
[j] Characterized by an intense itching sensation with or without rash.
[k] Mild or localized.
[l] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[m] Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.
[n] Including topical products that have the following active ingredients: hydrocortisone 0.5% or 1%, diphenhydramine, pramoxine, camphor, menthol.

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

DERMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[f]
Bullous dermatitis[l,o]	Urgent dermatology consultation: if unavailable, consider skin biopsy[q] and/or serum testing[r]	Mild (G1)[s]	• Consider holding immunotherapy[h] • High-potency topical steroids[g] to affected areas
		Moderate (G2)[t]	• Hold immunotherapy until <G1[h] • Prednisone/IV methylprednisolone 0.5–1 mg/kg/day[i] • If no improvement after 3 days, urgent consultation to dermatology ▸ If no access to dermatology, consider inpatient care with dermatology access • If diagnosis of bullous pemphigoid is confirmed by biopsy or serology, consider rituximab[w] or dupilumab[x]
		Severe (G3)[u] OR Life-threatening (G4)[v]	• Discontinue immunotherapy[h] • Prednisone/IV methylprednisolone 1–2 mg/kg/day[i] • If bullous pemphigoid confirmed, dupilumab[x] is recommended as a steroid-sparing measure • Consider alternative steroid-sparing options such as IVIG[y,z] as an adjunct to rituximab[w] • Inpatient care required • Urgent dermatology consultation
Stevens-Johnson syndrome (SJS)[p] or Toxic epidermal necrolysis (TEN)[p]	Urgent dermatology consultation: if unavailable, consider skin biopsy		• Discontinue immunotherapy[h] • Evaluate entire medication list for alternative culprit drug such as an antibiotic or anticonvulsant • Urgent dermatology, ophthalmology, and urology consultation • Prednisone/IV methylprednisolone 1–2 mg/kg/day[i] • Consider IVIG[z] • Other immunosuppressive therapies[aa] • Inpatient care required

Footnotes on ICI_DERM-3A

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

FOOTNOTES

[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Treat until symptoms improve to grade ≤1, then taper over 4–6 weeks.
[l] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[o] Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid. The most common irAE reported is bullous pemphigoid.
[p] SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
[q] Skin biopsies should be performed on perilesional intact skin. Two biopsies should be performed with one being sent for direct immunofluorescence testing in Michel's medium, if available, or in normal saline (if Michel's medium not available).
[r] The following serologic tests may be considered for autoimmune/irAE-associated bullous disorders: bullous pemphigoid antibodies, desmoglein 1 and 3 (pemphigus) antibodies, indirect immunofluorescence (anti-skin antibodies).
[s] Asymptomatic; blisters covering <10% BSA.
[t] Blisters covering 10%–30% BSA; painful blisters; limiting iADLs.
[u] Blisters covering >30% BSA; limiting self-care ADLs.
[v] Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated.
[w] 1000 mg once every 2 weeks for 2 doses (in combination with a tapering course of glucocorticoids), followed by maintenance of rituximab 500 mg at months 12 and 18 as needed. Joly P, et al. Lancet 2017;389:2031-2040.
[x] Shipman WD, et al. Br J Dermatol 2023;189:339-341.
[y] Ahmed AR. J Am Acad Dermatol 2001;45:825-835.
[z] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[aa] Immunosuppressive therapies (ie, etanercept, cyclosporine) can be considered. After a patient has widespread skin separation (blisters or erosions), the risk of infection should be weighed against the potential benefits of immunosuppression.

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

DERMATOLOGIC ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT[f]**

Lichen planus and lichenoid diseases[bb,cc] →
- Physical examination
- Oral and mucosal evaluation
- Consider skin biopsy
- Consider dermatology consultation

Mild: <10% BSA →
- Continue immunotherapy and assess response to topical steroid
- High-potency topical steroid[g,dd] or Tacrolimus 0.1% ointment

Moderate: 10%–30% BSA or not responsive to high-potency topical steroids →
- Hold immunotherapy[h]
- High-potency topical steroid[g,dd] or Tacrolimus 0.1% ointment
- Oral antihistamines
- Prednisone 0.5–1 mg/kg/day[ee]
- Consider referral to dermatology
- Narrow-band UVB phototherapy, if available and feasible
- If not responsive, treat as severe

Severe: >30% BSA →
- Hold immunotherapy[h]
- High-potency topical steroid[g,dd] or Tacrolimus 0.1% ointment
- Prednisone/IV methylprednisolone at 0.5–1 mg/kg/day[ee]
- Consider:
  - Referral to dermatology
  - Steroid-sparing immunosuppressants[ff]
  - Acitretin (if no childbearing potential)
  - Dupilumab

[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[bb] Shi VJ, et al. JAMA Dermatol 2016;152:1128-1136; Masterson WM, et al. Cancer Treat Res Commun 2022;30:100506.
[cc] Violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, significant pruritus. Erosions and striae (white lines intersecting) in the oral and vulvar mucosa.
[dd] Consider gel for mucosal disease, solution for scalp disease, and cream/lotion/ointment for other affected areas.
[ee] Treat until symptoms improve to grade 1 then taper over 3 weeks.
[ff] Azathioprine, cyclosporine, hydroxychloroquine, methotrexate, and mycophenolate mofetil.

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

DERMATOLOGIC ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT**[f]

Psoriasis and psoriasiform diseases[gg,hh] →
- Physical examination
- Consider oral and dental evaluation
- Consider skin biopsy
- Consider dermatology consultation

Mild: <10% BSA →
- Continue immunotherapy
- High-potency topical steroids[g]
- Consider transitioning to non-steroidal topical therapies such as tacrolimus 0.1% or calcipotriene 0.005% for long-term management in intertriginous areas or facial locations

Moderate: 10%–30% BSA or not responsive to high-potency topical steroids →
- Hold immunotherapy[h]
- High-potency topical steroids[g]
- Consider transitioning to non-steroidal topical therapies such as tacrolimus 0.1% or calcipotriene 0.005% for long-term management in intertriginous areas or facial locations
- Narrow-band UVB phototherapy, if available and feasible
- Consider:
  - Apremilast
  - Acitretin (if no childbearing potential)
- Refer to dermatology for consideration of approved biologics[ii]
- If not responsive, treat as severe

Severe: >30% BSA →
- Hold immunotherapy[h]
- High-potency topical steroids[g]
- Consider transitioning to non-steroidal topical therapies such as tacrolimus 0.1% or calcipotriene 0.005% for long-term management in intertriginous areas or facial locations
- Narrow-band UVB phototherapy, if available and feasible
- Consider:
  - Apremilast
  - Acitretin (if no childbearing potential)
  - Cyclosporine
  - Methotrexate
- Refer to dermatology for consideration of approved biologics[ii]

[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[gg] Nikolaou V, et al. J Am Acad Dermatol 2021;84:1310-1320; Said JT, et al. J Am Acad Dermatol 2022;87:399-400.
[hh] Thick, red scaly plaques, accentuated on extensor surfaces, scalp, umbilicus, and postauricular surfaces.
[ii] Anti-TNF, IL-23, or IL-17 inhibitors.

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

ORAL MUCOSA ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[f]
Oral mucosa inflammation[jj]	• Comprehensive mucosal exam • Assess for primary diagnosis and evaluate for skin blistering[kk] • Pain score/ alimentation limitations • Consider mucosal biopsy for histopathology and direct immunofluorescence • Consider infectious causes of oral inflammation and ulcers including herpes simplex virus (HSV) polymerase chain reaction (PCR) and fungal culture • Assess contribution of cytotoxic agents in combination regimens	General	• Dietary modifications, nutritional evaluation and supplementation[ll] • Good oral hygiene (eg, chlorhexidine oral rinse) • Topical anti-inflammatory agents (oral liquid [for swish and spit] or gel formulation)[mm] ‣ If progressive or not responsive after 1 month, consider initiating steroid-sparing immunosuppressants such as methotrexate or mycophenolate mofetil • If available, referral to: ‣ Dermatology ‣ Dental/Oral pathology[nn] ‣ Ear, nose, and throat (ENT)[oo]
		Mild (G1): some food restrictions	• Continue immunotherapy • Consider acid suppression[pp] • Consider intralesional steroids for localized mucositis (ulcers) recalcitrant to topical steroids • Topical anesthetics[qq]
		Moderate (G2): soft/pureed foods only	• Hold immunotherapy[h] • Consider intralesional steroids for localized mucositis (ulcers) recalcitrant to topical steroids • Prednisone or IV methylprednisolone 0.5–1 mg/kg/day[ee] • Lip/oral biopsy, if clinically indicated and not previously done
		Severe (G3–4): unable to eat	• Hold immunotherapy[h] • Inpatient care • Prednisone or IV methylprednisolone 1–2 mg/kg/day[ee] • Lip/oral biopsy, if clinically indicated and not previously done

Footnotes on ICI_DERM-6A

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

FOOTNOTES

[f] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[ee] Treat until symptoms improve to grade 1 then taper over 3 weeks.
[jj] Irritated gums and/or oropharynx, red/white lesions and/or ulcers, lichen planus, or mucositis; for management of lichen planus, see ICI_DERM-4.
[kk] The following serologic tests may be considered for autoimmune/irAE-associated blistering disease pemphigus (anti-desmoglein 1 and 3) and bullous pemphigoid (anti-bullous pemphigoid antigen 1 and 2). If immunologic tests confirm autoimmune disease, see blistering disorders on ICI_DERM-3.
[ll] Avoid crunchy, spicy, acidic, or hot food/drink as appropriate for comfort.
[mm] Dexamethasone 0.5 mg/5 mL solution; compounded budesonide 3 mg/10 mL solution; or high- or super-high-potency topical corticosteroids such as fluocinonide 0.05% gel, clobetasol 0.05% gel, augmented betamethasone dipropionate 0.05% gel, or a nonsteroidal anti-inflammatory such as tacrolimus 0.1% ointment.
[nn] To ensure adequate hygiene and protect against the risk of dental caries; consider if mild and strongly consider if moderate or severe inflammation.
[oo] Assist in the management of persistent mucositis or if oropharynx/larynx involved; consider if mild or strongly consider if moderate or severe (especially if airway involved).
[pp] Proton pump inhibitor (PPI) or H2 blockade.
[qq] Magic mouthwash (equal parts diphenhydramine, antacid, and viscous lidocaine).

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

ORAL MUCOSA ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT[f]**

Dry mouth (Sicca syndrome[rr]) →

- Review medication profile and avoid medications that contribute to dry mouth if possible
- Assess hydration status
- Check salivary pooling in floor of mouth
- Assess thickness of saliva
- Evaluate dentition and gum recession
- Anti-SS-A and anti-SS-B

Mild (G1)[tt] →
- Continue immunotherapy
- Dietary modifications[ll]
- Improve hydration and limit caffeine intake
- Topical comfort measures (water sips, saliva substitutes, and moisture-preserving, non-alcoholic mouth rinses, sprays, or children's toothpaste)
- Salivary stimulants (sugarless chewing gum, lozenges, or candy)

Moderate (G2)/severe (G3)[uu] →
- Hold immunotherapy[h]
- Dietary modifications[ll]
- Additional topical measures (saliva substitutes, mouth rinses or sprays)
- Prednisone at 20–40 mg daily for 2–4 weeks, then taper[xx]
- Systemic sialagogues (cevimeline or pilocarpine)
- Rheumatology referral
- Dental referral[yy] or oral pathology if available
- Consider inpatient care for severe cases

Oral dysesthesia[ss] →

- Assess location and character of pain
- Rule out odontogenic or mucosal source
- Assess severity of pain and impact on function

Mild (G1)[vv] →
- Continue immunotherapy
- Dietary modifications[ll]
- Topical steroids (gel or rinse preferred) or viscous lidocaine

Moderate (G2)/severe (G3)[ww] →
- Hold immunotherapy[h]
- Dietary modifications[ll]
- Gabapentin, high-potency topical steroids (gel or rinse preferred), or viscous lidocaine

Footnotes on ICI_DERM-7A

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

FOOTNOTES

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

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

ENDOCRINE ADVERSE EVENT(S)

Hyperglycemia[a,b]
- New-onset fasting glucose >200 mg/dL[c] OR
- Random blood glucose >250 mg/dL OR
- History of type 2 diabetes mellitus (DM) with fasting/random glucose >250 mg/dL

→

DIAGNOSIS/WORKUP[d]
- Consider new-onset ICI-associated type 1 DM (ICI-T1DM)[e]
- C-peptide with repeat serum glucose
- Evaluate for DKA[f] per institutional guidelines
  - Blood pH, basic metabolic panel, urine or serum ketones (eg, beta hydroxybutyrate)
- If fatigue or other endocrine irAEs, evaluate for hypophysitis/adrenal insufficiency (see ICI_ENDO-3)
- Consider measurement of autoantibodies (eg, anti-GAD, anti-islet cell, IA-2, anti-insulin, ZnT8)[e]

MANAGEMENT[g,h]

C-peptide low (consistent with ICI-T1DM)[e,g,h,i,j]
- DKA present →
  - Urgent endocrine consultation
  - Inpatient care
  - Hold immunotherapy until DKA resolves[k]
  - Manage DKA as per institutional guidelines[l]
  - Initiate insulin, as directed by inpatient team or endocrinologist, and close glucose monitoring (consider early use of continuous glucose monitoring [CGM])
- DKA not present →
  - Urgent endocrine consultation, consider inpatient care
  - Initiate insulin and close glucose monitoring consistent with T1DM, as directed by endocrinologist
  - Continue immunotherapy

C-peptide appropriate for serum glucose →
- Continue monitoring of serum glucose and consider HbA1c
- Continue immunotherapy
- Consider insulin resistance (T2DM) or steroid-related[d] hyperglycemia
- Medical therapy, diet, and lifestyle interventions as per institutional guidelines

[a] Elevated fasting glucose <200 mg/dL should be managed per national/institutional guidelines and/or by a patient's primary care physician (PCP) or endocrinologist.
[b] Fasting glucose is preferred.
[c] In patients who are critically ill/ill-appearing with glucose >200 mg/dL (typically 300–500 mg/dL), urgent/emergent evaluation for DKA is indicated.
[d] High-dose steroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.
[e] The development of ICI-T1DM can be life-threatening if insulin therapy is not provided. Once new T1DM is diagnosed, management and monitoring should be directed by endocrinology team. ICI-T1DM may be permanent. Autoantibodies are not required for diagnosis. Empiric treatment as T1DM recommended if C-peptide unknown.
[f] Symptoms of DKA may include excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath.
[g] Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplement if needed.
[h] Insufficient evidence to suggest steroids may reverse ICI-T1DM, and may complicate glycemic control.
[i] Repeat C-peptide once euglycemic to confirm diagnosis of ICI-T1DM and insulin dependence.
[j] Patients with ICI-T1DM and/or ICI-hypophysitis with adrenal insufficiency are recommended to wear a medical alert bracelet, ensure adequate supply of medications if traveling, and notify their oncologist or endocrinologist in advance of scheduled procedures or in case of acute illness as medication doses may need to be adjusted.
[k] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[l] Institutional guidelines may include but are not limited to: IV fluids +/– potassium supplementation, IV insulin, hourly glucose, serum ketones, blood pH, and anion gap.

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

ENDOCRINE ADVERSE EVENT(S) | **ASSESSMENT** | **MANAGEMENT**

Hypothyroidism → Monitor TSH, FT4 every 4–6 weeks[m]
- If TSH elevated, proceed based on TSH levels as follows or repeat TSH, FT4 in 4–6 weeks

→ **Subclinical hypothyroidism**
- TSH between 4 to <10
- Normal FT4
- Patient asymptomatic

→ Management:
- Continue immunotherapy
- Continue to monitor thyroid function tests (TFTs)

OR
- Elevated TSH (>10)
- Normal FT4

→ Management:
- Continue immunotherapy
- Consider levothyroxine if elevated TSH persists. If patient becomes symptomatic, treat as overt hypothyroidism

→ **Overt hypothyroidism**
- Elevated TSH
- Low FT4

→ Management:
- Consider endocrine consultation
- Check serum cortisol to exclude coexistent adrenal insufficiency prior to treatment
- Initiate thyroid hormone supplementation with levothyroxine[n]
  - Repeat TSH in 4–6 weeks to guide dosing changes
- Continue immunotherapy once adrenal insufficiency is ruled out and replacement endocrine therapy has started

→ **Central hypothyroidism**
- Normal or low TSH
- Low FT4

→ Management: Hypophysitis/Central hypothyroidism (ICI_ENDO-3); exclude recovery from thyrotoxicosis and non-thyroidal illness

Thyrotoxicosis[o,p] →
- Low or suppressed TSH with high FT4/total T3
- Consider endocrine consultation if symptomatic

→ Management:
- Continue immunotherapy if asymptomatic
- Consider propranolol (10–20 mg every 4–6 hours for symptoms as needed) or atenolol or metoprolol as needed for symptoms until thyrotoxicosis resolves
- Repeat TFTs in 4–6 weeks
  - If resolved, no further therapy for thyrotoxicosis. Thyrotoxicosis often evolves to hypothyroidism (50%–90%) requiring treatment with thyroid hormone replacement (see Overt hypothyroidism above for levothyroxine dosing)
  - If persistent thyrotoxicosis, consider evaluation for Graves' disease.[q]

Footnotes on ICI_ENDO-2A

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

FOOTNOTES

[m] For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase TFT interval to every 12–18 weeks as indicated.
[n] Levothyroxine oral 1.2–1.4 mcg/kg/day. For patients with advanced age, cardiac risk, or prolonged hypothyroidism, initiate at 0.8–1.0 mcg/kg/day. If marked/profound hypothyroidism at diagnosis, give a double dose of levothyroxine for 2–3 days when initiating therapy.
[o] Defined as suppressed TSH that may be: a) subclinical if FT4 normal; or b) clinical if high FT4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis. Most patients with thyrotoxicosis are asymptomatic. Symptoms, if present, may include palpitations, heat intolerance, restlessness or anxiety, fine tremor, and/or weight loss. Consider thyroid autoantibodies (eg, anti-thyroid peroxidase [TPO] and anti-thyroglobulin [Tg]), but correlation with checkpoint inhibitor thyroiditis remains unknown.
[p] Thyrotoxicosis in this setting is usually from a destructive process, and thus anti-thyroid drugs (eg, methimazole, propylthiouracil) are not recommended. ICI-induced thyrotoxicosis usually evolves into hypothyroidism and requires replacement therapy, but sometimes resolves to normal with long-term follow-up.
[q] Usual duration of thyrotoxicosis from checkpoint immunotherapy is 4–6 weeks. Graves' disease evaluation with TSH receptor antibody (TRAb) or thyroid-stimulating Ig (TSI) measurement or thyroid uptake scan can be considered in patients with persistent thyrotoxicosis. Recommend referral to endocrinology.

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

ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT
Hypophysitis[j,r] →	• Evaluate for symptoms[r,s] • Cortisol and ACTH (morning preferred),[t] TSH, FT4, serum Na • Consider LH, FSH, and sex hormones as appropriate • Cosyntropin stimulation testing is not recommended in acute settings[s,u] • Brain MRI ± contrast with pituitary/sellar cuts, especially if mass effect symptoms or concern for metastatic disease[r,v]	→ • Endocrine consultation and patient education • Hold immunotherapy[k] until acute symptoms resolve and hormone replacement is initiated • If severe symptoms with concern for mass effect, may consider high-dose steroids[w] • Treat with physiologic hormone replacement[x,y,z] • Secondary adrenal insufficiency (low ACTH, low cortisol) ‣ Physiologic steroids in ambulatory patients and stress dosing for acute illness or surgery/procedures[j,x] • Central hypothyroidism (normal or low TSH, low FT4) ‣ Thyroid hormone replacement, titrate to FT4 level[y]
Primary adrenal insufficiency (high ACTH with low morning cortisol, abnormal cosyntropin stimulation test) →	• Rare diagnosis that is not usually associated with checkpoint immunotherapy • If there is concern for this diagnosis, recommend endocrine consultation	

Footnotes on ICI_ENDO-3A

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

FOOTNOTES

[j] Patients with ICI-T1DM and/or ICI-hypophysitis with adrenal insufficiency are recommended to wear a medical alert bracelet, ensure adequate supply of medications if traveling, and notify their oncologist or endocrinologist in advance of scheduled procedures or in case of acute illness as medication doses may need to be adjusted.

[k] Principles of Immunotherapy Rechallenge (IMMUNO-C).

[r] Hypophysitis typically presents with acute or subacute symptoms from pituitary hormone loss, notably adrenal insufficiency including dizziness, nausea/emesis, anorexia, severe fatigue, confusion, lethargy, and/or low blood pressure. Labs show low serum ACTH and cortisol, and sometimes low serum sodium or abnormalities of other pituitary hormones. Some patients present with symptoms from mass effect of pituitary enlargement (eg, headache, vision change), more often with anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) therapies.

[s] Cosyntropin stimulation testing can be normal in acute secondary adrenal insufficiency and would not exclude hypophysitis.

[t] For preoperative patients who had neoadjuvant therapy and cortisol status is unknown, consider a random cortisol. If <2 mcg/dL, treat. If between 2 mcg/dL and 5 mcg/dL, treat and refer to endocrinology.

[u] In patients who have had chronic steroid exposure from their regimen or have questionable cortisol levels, send for cosyntropin stimulation in the outpatient setting.

[v] Hypophysitis from anti-PD-1/PD-L1 therapy may not show classic pituitary enlargement and enhancement on MRI as seen with anti-CTLA-4–associated hypophysitis. Consider imaging if diabetes insipidus present as rarely seen in isolated ICI-hypophysitis.

[w] If concern for optic chiasm compression or mass effect from hypophysitis, may consider high-dose steroids (eg, IV methylprednisolone 1 mg/ kg/day) as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement. High-dose steroids do not reverse the likelihood of permanent hormone deficit and if prolonged, may have negative impact on outcomes.

[x] Preferred treatment for adrenal insufficiency is with hydrocortisone, dosed at 20 mg PO every AM and 10 mg PO in the early afternoon for ambulatory patients. Dosing for physiologic replacement is considered higher in patients on immunotherapy due to underlying inflammation. Further titration is best guided by an endocrinologist. Once-daily prednisone at an equivalent dose is an alternative regimen. Acutely symptomatic or hospitalized patients or patients undergoing surgery with general anesthesia require stress dose steroids (hydrocortisone 100 mg IV x 1, then 50 mg every 8 hours, tapered based on clinical parameters) and endocrinology consultation. Patients should double their dose for 3 days for mild illness or fever in the outpatient setting. Patients typically require cortisol replacement indefinitely.

[y] See Overt hypothyroidism on ICI_ENDO-2 for levothyroxine dosing.

[z] For central hypogonadism (low LH, low FSH, and low sex hormone, not due to underlying illness) may consider testosterone supplementation in individuals and estrogen in premenopausal individuals if not otherwise contraindicated.

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

ADVERSE EVENT(S)	ASSESSMENT	SUSPECTED DIAGNOSES	
Fatigue →	• Evaluate for and rule out other non-ICI–related etiologies of fatigue • Physical exam including vital signs (weight, temperature, heart rate, respiratory rate [RR], blood pressure, oxygen saturation [rest and walking]) • Lab tests ‣ CBC ‣ CMP ‣ TSH, FT4 (if not done recently) ‣ Morning cortisol ‣ Morning ACTH (if morning cortisol subnormal) ‣ Morning testosterone ‣ CK and cardiac enzymes • Medication review • Assess for depression (consider PHQ-9)[a]	→ Myocarditis	→ ICI_CARDIO-1
		→ Hyperglycemia-related DKA	→ ICI_ENDO-1
		→ Hypothyroidism/thyrotoxicosis	→ ICI_ENDO-2
		→ Hypophysitis/primary adrenal insufficiency	→ ICI_ENDO-3
		→ Unexplained drop in hemoglobin	→ ICI_HEM-1
		→ Myositis	→ ICI_MS-3
		→ Pneumonitis	→ ICI_PULM-1

[a] NCCN Guidelines for Distress Management.

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

UPPER GASTROINTESTINAL ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT
Esophagitis/ Gastritis/ Duodenitis[a] →	• Screen for risk factors that may contribute to symptoms (eg, narcotics, anti-motility agents, nonsteroidal anti-inflammatory drugs [NSAIDs], certain cancer therapies, celiac disease) • If symptoms are moderate to severe,[b] consider the following: ‣ Esophagogastroduodenoscopy (EGD) evaluation[c] to rule out different etiologies ◊ Infectious pathogens: *Candida,* cytomegalovirus (CMV), HSV, *H. pylori*, etc. ◊ Inflammation of esophagus, stomach, and duodenum ‣ Motility evaluation	Mild[d] →	• Continue immunotherapy • Supportive measures including: ‣ Hydration, anti-nausea medication, dietary modification • Consider sucralfate, proton pump inhibitors (PPIs), oral analgesics • Eliminate risk factors when possible
		Moderate to Severe[b] →	• Consider holding immunotherapy[e] • Supportive measures as per management for Mild (above) • Consider inpatient management • GI consultation • Prednisone/IV methylprednisolone (1 mg/kg/day) or oral budesonide[f] (open capsule) ‣ If no improvement and not already done, consider biologic treatment (eg, infliximab,[g,h,i] vedolizumab[h]) • For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease)

[a] Symptoms of upper GI AEs include nausea, vomiting, dysphagia, odynophagia, reflux, hematemesis, dyspepsia, melena, anorexia, early satiety, bloating, iron deficiency anemia, abdominal pain, diarrhea, and weight loss.
[b] Symptomatic, unable to eat regular diet, exhibits dehydration, weight loss, hemodynamic instability. Aggressive intervention is needed.
[c] 10%–20% of patients will have normal endoscopic evaluation but positive biopsies for ICI gastritis. Haryal A, et al. Cancer 2023;129:367-375.
[d] Symptomatic, but able to eat regular diet or maintain weight and hydration status. No aggressive intervention indicated.
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] 9 mg/day for 2 weeks, then taper down by 3 mg every week for total 4 weeks.
[g] Start infliximab at 5 mg/kg.
[h] Perform ID screening (HIV; hepatitis A, B, C) and TB blood test (eg, T-Spot/QuantiFERON-TB Gold) (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.
[i] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.

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

GASTROINTESTINAL ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT**[p]

- **Diarrhea**
- **Colitis**[j]

Mild (G1)[k] →
- **Consider stool evaluation to rule out infectious etiology**[n]
  - ***C. difficile***
  - **Nucleic acid amplification tests (NAATs) for GI pathogens (other bacteria, viruses)**
  - **In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia, Cryptosporidium* spp, *E. histolytica,* microsporidia, and *Cyclospora/isospora spp***
- **Fecal calprotectin ± lactoferrin**[o]

→
- **Hydration**
- **Close monitoring**[q]
- **Dietary modifications**[r]
- **Consider holding immunotherapy**[e]
- **Consider loperamide or diphenoxylate/atropine for 2–3 days as an adjunct for symptom relief**
  - **If no improvement and not already done, obtain lab tests for infectious workup**
  - **Caution is warranted to avoid masking symptoms; discontinue antidiarrheals if diarrhea persists, to assess response to immunosuppressive therapy**
- **If persistent or progressive symptoms, check lactoferrin/calprotectin**
  - **If positive, treat as G2**
  - **If negative and no infection, continue G1 management and consider adding mesalamine and/or cholestyramine**

Moderate (G2)[l] → ICI_GI-3

Severe (G3–4)[m] → ICI_GI-4

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, and nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including PUD and malignant bleeding.
[k] Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[l] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[m] More than 6 bowel movements above baseline per day, colitis symptoms, interference with ADLs, hemodynamic instability, hospitalization, serious complications (eg, ischemic bowel, perforation, toxic megacolon), or other colitis-related life-threatening conditions.
[n] It is not necessary to wait for test results before providing therapy to manage irAEs.
[o] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.
[p] Principles of Immunosuppression (IMMUNO-A).
[q] Eg, stool frequency, consistency, blood in stool, nocturnal symptoms, weight trend. If progressive, consider stool evaluation to rule out infectious etiology.
[r] Consider lactose-free, low-fiber diet until diarrhea subsides. Consider BRAT (bananas, rice, apple sauce, toast) diet.

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

GASTROINTESTINAL ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[p]
• Diarrhea • Colitis[j] Moderate (G2)[l]	• Stool evaluation to rule out infectious etiology[n] ‣ *C. difficile* ‣ NAATs for GI pathogens (other bacteria, viruses) ‣ In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia, Cryptosporidium* spp, *E. histolytica,* microsporidia, and *Cyclospora/isospora spp* • Fecal calprotectin ± lactoferrin[o] • Consider abdominal/pelvic CT with contrast[s] • Consider GI consultation ‣ Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy[o]	• Hold immunotherapy[e] • For pathologically confirmed microscopic colitis, consider budesonide 9 mg daily prior to systemic steroids[t] • Prednisone/IV methylprednisolone[u,v] (1–2 mg/kg/day)[w] • If no response to oral steroids after 3 days, consider IV steroids: ‣ If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,[x] consider adding infliximab[g,h,i,y] or vedolizumab[h,y,z] ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[aa] • For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease) • For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

Footnotes on ICI_GI-3A

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

FOOTNOTES

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Start infliximab at 5 mg/kg.
[h] Perform ID screening (HIV; hepatitis A, B, C) and TB blood test (eg, T-Spot/QuantiFERON-TB Gold) (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.
[i] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.
[j] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, and nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including PUD and malignant bleeding.
[l] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[n] It is not necessary to wait for test results before providing therapy to manage irAEs.
[o] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.
[p] Principles of Immunosuppression (IMMUNO-A).
[s] In cases with high suspicion for complications (eg, toxic megacolon, abscess, perforation).
[t] Hughes MS, et al. J Immunother Cancer 2019;7:292.
[u] IV steroid is preferred due to possible absorption impairment.
[v] Convert to prednisone when appropriate.
[w] Treat until symptoms improve to grade ≤1, then taper over <4 to 6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <2 to 4 weeks should be made to minimize the complication of infection. If strong clinical suspicion for ICI diarrhea, start empiric IV steroids while waiting for EGD/colonoscopy/flexible sigmoidoscopy results.
[x] For patients with severe colitis such as ulcerations on colonoscopy/flexible sigmoidoscopy, higher rates of refractory response to steroids have been reported. Early introduction of infliximab or vedolizumab can be considered to reduce recurrence.
[y] Duration of therapy with infliximab or vedolizumab is not clearly defined; however, receipt of ≥3 doses (at weeks 0, 2, and 6) has been associated with less frequent colitis recurrence. Repeat endoscopy and/or fecal calprotectin to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A).
[z] Zou F, et al. J Immunother Cancer 2021;9:e003277.
[aa] Esfahani K, et al. N Engl J Med 2020;382;2374-2375; Thomas AS, et al. N Engl J Med 2021;384:581-583; Bishu S, et al. Gastroenterology 2021;160:932-934; Shirwaikar Thomas A, et al. Am J Gastroenterol 2023;118:1679-1683.

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

GRADING	ASSESSMENT/GRADING	MANAGEMENT[p]
• Diarrhea • Colitis Severe (G3–4)[m] →	• Stool evaluation to rule out infectious etiology[n] ‣ *C. difficile* ‣ NAATs for GI pathogens (other bacteria, viruses) ‣ In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia, Cryptosporidium* spp, *E. histolytica,* microsporidia, and *Cyclospora/isospora spp* • Fecal calprotectin ± lactoferrin[o] • Consider abdominal/pelvic CT with contrast[s] • Recommend GI consultation ‣ Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy[o] →	• G3: If using combination IO therapy, discontinue current therapy[e] • G4: Discontinue immunotherapy agent responsible for toxicity[e] • Consider inpatient care for provision of supportive care • IV methylprednisolone[v] (1–2 mg/kg/day)[w] • If no response in 1–2 days or unable to transition to oral steroids, additional immunosuppression required ‣ If colonoscopy or flexible sigmoidoscopy shows significant ulceration, non-ulcerative inflammation, or microscopic colitis on histology,[x] continue steroids and strongly consider adding infliximab[g,h,i,y] or vedolizumab[h,y,z,aa] ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[aa] • For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease) • For immunosuppressant-refractory colitis, fecal transplantation may be considered based on institutional availability and expertise

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Start infliximab at 5 mg/kg.
[h] Perform ID screening (HIV; hepatitis A, B, C), and TB blood test (eg, T-Spot/QuantiFERON-TB Gold) (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.
[i] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.
[m] More than 6 bowel movements above baseline per day, colitis symptoms, interference with ADLs, hemodynamic instability, hospitalization, serious complications (eg, ischemic bowel, perforation, toxic megacolon), or other colitis-related life-threatening conditions.
[n] It is not necessary to wait for test results before providing therapy to manage irAEs.
[o] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.
[p] Principles of Immunosuppression (IMMUNO-A).
[s] In cases with high suspicion for complications (eg, toxic megacolon, abscess, perforation).
[v] Convert to prednisone when appropriate.
[w] Treat until symptoms improve to grade ≤1, then taper over <4 to 6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <2 to 4 weeks should be made to minimize the complication of infection. If strong clinical suspicion for ICI diarrhea, start empiric IV steroids while waiting for EGD/colonoscopy/flexible sigmoidoscopy results.
[x] For patients with severe colitis such as ulcerations on colonoscopy/flexible sigmoidoscopy, higher rates of refractory response to steroids have been reported. Early introduction of infliximab or vedolizumab can be considered to reduce recurrence.
[y] Duration of therapy with infliximab or vedolizumab is not clearly defined; however, receipt of three or more doses (at weeks 0, 2, and 6) has been associated with less frequent colitis recurrence. Repeat endoscopy and/or fecal calprotectin to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A).
[z] Zou F, et al. J Immunother Cancer 2021;9:e003277.
[aa] Esfahani K, et al. N Engl J Med 2020;382;2374-2375; Thomas AS, et al. N Engl J Med 2021;384:581-583. Bishu S, et al. Gastroenterology 2021;160:932-934; Shirwaikar Thomas A, et al. Am J Gastroenterol 2023;118:1679-1683.

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

HEPATOBILIARY ADVERSE EVENT(S) | **ASSESSMENT/GRADING[bb,cc]** | **MANAGEMENT[p]**

Elevated ALT/AST →

- Rule out viral etiology,[dd] disease-related hepatic dysfunction, and alternative causes of drug-induced liver injury
  - Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)
- Consider CK, aldolase, and ferritin to rule out other causes of elevated ALT/AST (eg, myositis [ICI_MS-3], myocarditis [ICI_CARDIO-1], and HLH-like syndrome [ICI_HEM-4])
- Consider abdominal ultrasound
  - Contrast-enhanced CT/MRI may be considered if no response to treatment or if there is a cholestatic pattern of liver tests

G1
<3 x upper limit of normal (ULN) →
- Consider holding immunotherapy for concerning lab value trend[e]
- Perform liver tests[ee] with increased frequency

G2
3–5 x ULN →
- Hold immunotherapy[e]
- Perform liver tests[ee] every 3–5 days
- Monitor prothrombin time/international normalized ratio (PT/INR) periodically
- Consider prednisone 0.5–1 mg/kg/day[ff,gg]
  - If liver tests suggest worsening or no improvement after 3–7 days, treat as G3

G3
>5 to 20 x ULN
G4
>20 x ULN
→ ICI_GI-6

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Principles of Immunosuppression (IMMUNO-A).
[bb] Consider initiating steroids while waiting for results in cases of G4 ALT/AST elevations.
[cc] Hyperbilirubinemia of hepatic origin is generally of conjugated predominance (or conjugated hyperbilirubinemia).
[dd] Consider testing for viral infections based on liver test pattern, viral risk factors, and clinical presentation including hepatitis B surface antigen (HBsAg).
[ee] ALT, AST, alkaline phosphatase, bilirubin (total and direct), and albumin.
[ff] Prednisone with maximum dose of 60 mg/day has been shown to be effective in autoimmune hepatitis. Mack CL, et al. Hepatology 2020;72:671-722.
[gg] When liver tests show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.

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

HEPATOBILIARY ADVERSE EVENT(S)

- Elevated ALT/AST
  - G3
    >5 to 20 x ULN
  - G4
    >20 x ULN
- Concomitant elevated bilirubin (>2 mg/dL) increases risk of hepatic failure (unless known Gilbert syndrome)

→

ASSESSMENT/GRADING[bb,cc]

- See Assessment on ICI_GI-5
- Recommend GI/hepatology evaluation

MANAGEMENT[p,hh]

General (G3 or G4) →
- Monitor PT/INR weekly or more often if clinically indicated based on liver tests and patient condition
- Consider diagnostic parenchymal liver biopsy if no contraindications
  - Reserve for atypical (cholestatic) clinical/biochemical presentation or when there is no response to standard therapy

G3 →
- Hold immunotherapy[e]
- Initiate prednisone/IV methylprednisolone 0.5–1 mg/kg/day[ff,gg]
  - If no improvement after 1–2 days, consider adding mycophenolate mofetil or tacrolimus[ii]
    - ◊ If refractory to mycophenolate mofetil or tacrolimus, consider tocilizumab or other steroid-sparing immunosuppressive therapy[jj,kk]
  - Urgent GI/hepatology referral if no improvement after 7 days of treatment or if 2 immunosuppressive agents do not yield adequate response within an additional 7 days
- Consider inpatient care, particularly if synthetic hepatic dysfunction is observed[ll]
- Perform liver tests[ee] every 1–5 days depending on magnitude and rate of change

G4 →
- Discontinue immunotherapy[e]
- Initiate prednisone/IV methylprednisolone 0.5–1 mg/kg/day[ff,gg,mm]
  - If no improvement after 1–2 days, consider adding mycophenolate mofetil or tacrolimus[ii]
    - ◊ If refractory to mycophenolate mofetil or tacrolimus, consider tocilizumab or other steroid-sparing immunosuppressive therapy[jj,kk]
  - Urgent GI/hepatology referral if no improvement after 7 days of treatment or if 2 immunosuppressive agents do not yield adequate response within an additional 7 days
- Inpatient care, particularly if synthetic hepatic dysfunction is observed[ll]
- Perform liver tests[ee] every 1–3 days

Footnotes on ICI_GI-6A

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

FOOTNOTES

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Principles of Immunosuppression (IMMUNO-A).
[bb] Consider initiating steroids while waiting for results in cases of G4 ALT/AST elevations.
[cc] Hyperbilirubinemia of hepatic origin is generally of conjugated predominance (or conjugated hyperbilirubinemia).
[ee] ALT, AST, alkaline phosphatase, bilirubin (total and direct), and albumin.
[ff] Prednisone with maximum dose of 60 mg/day has been shown to be effective in autoimmune hepatitis. Mack CL, et al. Hepatology 2020;72:671-722.
[gg] When liver tests show sustained improvement or return to ≤G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.
[hh] Infliximab has been associated with drug-induced liver injury, particularly drug-induced autoimmune hepatitis.
[ii] Consider mycophenolate mofetil at a maximum dose of 1.5 g every 12 hours. Tacrolimus may be considered instead of mycophenolate mofetil in patients with concomitant diarrhea or leukopenia or added to mycophenolate mofetil in refractory cases. Monitor renal function and check single tacrolimus trough level 2 to 3 days after initiation and if dose is increased. Snijders RJALM, et al. J Hepatol 2024;80:576-585. There is no target tacrolimus trough level; target the lowest dose that induces a biochemical response. Taper serially, starting with medications with the highest toxicity first (typically prednisone).
[jj] Other steroid-sparing therapy may include ATG or azathioprine. Response to these agents may be delayed and may require prolonged therapy in the treatment of irAEs.
[kk] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating IL-6 inhibitors and use with caution in those patients.
[ll] A total bilirubin >2.5 mg/dL plus international normalized ratio (INR) >1.5, ascites, or encephalopathy. Hountondji L, et al. Aliment Pharmacol Ther 2024;60:1561-1572.
[mm] Consider early concomitant use of mycophenolate mofetil with the initiation of steroids.

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

HEPATOBILIARY ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT[p]**

Elevated alkaline phosphatase (predominant)[nn] with or without bilirubin/AST/ALT elevation[oo] →

- Rule out other drug-induced liver injury[pp]
- Rule out biliary obstruction or tumor infiltration of liver: consider magnetic resonance cholangiopancreatography (MRCP) or abdominal contrast-enhanced CT/MRI (ultrasound if contrast-enhanced CT/MRI contraindicated)[qq]
- Consider fractionating alkaline phosphatase, gamma-glutamyl transferase (GGT), or check 5'-nucleotidase to confirm alkaline phosphatase is of liver origin
- Consider liver biopsy for mixed (elevated ALT/AST and elevated alkaline phosphatase) pattern of liver injury or if no appreciable response to empiric treatment

G1
<2.5 x ULN (or baseline) →
- Consider holding immunotherapy
- Perform liver tests[ee] with increased frequency

G2
2.5–5 x ULN (or baseline) →
- Hold immunotherapy[e]
- Initiate prednisone 0.5–1 mg/kg/day[gg]
- Ursodiol 13–15 mg/kg/day[rr]
- Perform liver tests[ee] every 3–5 days
  - If alkaline phosphatase worsens or does not improve after 3 days, treat as G3
- Consider GI consultation

G3
5–20 x ULN (or baseline)
G4
>20 x ULN (or baseline) →
- Discontinue immunotherapy[e]
- Monitor PT/INR if there is a high suspicion for elevated bilirubin/AST/ALT
- Initiate prednisone/IV methylprednisolone 1 mg/kg/day[gg,mm]
- Ursodiol 13–15 mg/kg/day[rr]
  - If no improvement after 1–2 days, consider adding steroid-sparing immunosuppressive therapy[ii,kk,ss]
- Perform liver tests[ee] every 1–3 days
- GI consultation
- Consider inpatient monitoring dependent on clinical status

Footnotes on ICI_GI-7A

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

FOOTNOTES

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Principles of Immunosuppression (IMMUNO-A).
[ee] ALT, AST, alkaline phosphatase, bilirubin (total and direct), and albumin.
[gg] When liver tests show sustained improvement or return to ≤G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.
[ii] Consider mycophenolate mofetil at a maximum dose of 1.5 g every 12 hours. Tacrolimus may be considered instead of mycophenolate mofetil in patients with concomitant diarrhea or leukopenia or added to mycophenolate mofetil in refractory cases. Monitor renal function and check single tacrolimus trough level 2 to 3 days after initiation and if dose is increased. Snijders RJALM, et al. J Hepatol 2024;80:576-585. There is no target tacrolimus trough level; target the lowest dose that induces a biochemical response. Taper serially, starting with medications with the highest toxicity first (typically prednisone).
[kk] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating IL-6 inhibitors and use with caution in those patients.
[mm] Consider early concomitant use of mycophenolate mofetil with the initiation of steroids.
[nn] There is no predetermined alkaline phosphatase elevation. A predominant alkaline phosphatase elevation can be indicative of cholangitis.
[oo] If elevated AST and ALT levels, see ICI_GI-5.
[pp] Drug-induced cholestasis may include penicillins, trimethoprim-sulfamethoxazole (TMP-SMZ), macrolides, tetracycline, antifungals, antiretrovirals, anti-inflammatories, and psychotropes.
[qq] Endoscopic retrograde cholangiopancreatography (ERCP) can be considered.
[rr] Ursodiol is available in capsules (200 mg, 300 mg, 400 mg) and tablets (250 mg, 500 mg). Split dosing (BID or TID) with food should be considered to enhance absorption and minimize GI side effects.
[ss] Other steroid-sparing immunosuppressive therapy may include ATG, azathioprine, tacrolimus, or tocilizumab. Response to these agents may be delayed and may require prolonged therapy in the treatment of irAEs.

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

PANCREATIC ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT[p]**

Elevation in lipase (asymptomatic) →
- Assess for signs/symptoms of pancreatitis[tt]
- If clinical concern for pancreatitis, see ICI_GI-9

Mild
≤3 x ULN lipase →
- If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy[e]
- Evaluate for pancreatitis (ICI_GI-9)
  - If evidence of pancreatitis, manage according to pancreatitis algorithm (ICI_GI-9)
- Consider other causes for elevated lipase[uu]

Moderate
>3–5 x ULN lipase
or
Severe
>5 x ULN lipase →
- If isolated elevation of enzymes without evidence of pancreatitis, consider continuing immunotherapy[e]
- Evaluate for pancreatitis
  - Clinical assessment[vv]
  - If persistent moderate to severe lipase elevation, abdominal CT with contrast or MRCP
- Consider other causes for elevated lipase[uu]
- If evidence of pancreatitis, manage according to pancreatitis algorithm (ICI_GI-9)

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Principles of Immunosuppression (IMMUNO-A).
[tt] Mild symptoms of pancreatitis can include: nausea, bloating, belching, abdominal pain, or back pain.
[uu] Inflammatory bowel disease, irritable bowel syndrome, bowel obstruction, gastroparesis, nausea/vomiting, medications, alcohol, and/or DM.
[vv] Routine lipase assessments do not have to be performed outside of clinical suspicion of possible pancreatitis. See Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

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

PANCREATIC[ww] ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT[p]**

Acute pancreatitis[xx] →

- Assess for signs/symptoms of pancreatitis
- Abdominal CT with contrast
- Consider MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT
- Assess for other causes (ie, alcohol use, biliary)
- Assess for IgG4; If positive, manage as autoimmune pancreatitis

General →
- Evaluate for signs/symptoms of pancreatic exocrine insufficiency and/or DM; supplement if needed and monitor

Mild (G2)[yy] →
- Consider holding immunotherapy[e]
- Consider gastroenterology referral
- Consider IV hydration
- Manage as per elevation in lipase (asymptomatic) (ICI_GI-8)

Moderate (G3)[zz] →
- Hold immunotherapy[e]
- Gastroenterology referral
- IV hydration

Severe (G4)[aaa] →
- Permanently discontinue immunotherapy[e]
- Inpatient care
- Gastroenterology referral
- IV hydration

[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Principles of Immunosuppression (IMMUNO-A).
[ww] No requirement for routine monitoring of potential pancreatitis with imaging.
[xx] Provide standard medical care for signs and symptoms of acute pancreatitis, including hospital admission, aggressive fluid resuscitation, and pain control. Management and follow-up of pancreatitis should be directed by gastroenterology/pancreatic subspecialists.
[yy] Asymptomatic lipase elevation OR radiologic features on CT or clinical findings concerning for pancreatitis. The decision to hold immunotherapy is based on clinical suspicion. If lipase >3 x ULN or CT findings are prominent, holding immunotherapy is recommended.
[zz] Symptomatic pain or vomiting AND any lipase elevation or CT findings suggesting pancreatitis.
[aaa] Features of pancreatitis (enzyme elevation OR CT findings) with life-threatening consequences OR hemodynamic instability OR urgent intervention indicated.

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

HEMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT	SUSPECTED DIAGNOSES	
Unexplained drop in hemoglobin (Hb)[a] →	• Evaluate for common causes of anemia such as bleeding (eg, fecal occult blood test) and iron, B12, and folate deficiencies • CMP • CBC with differential • Evaluate for evidence of hemolysis: ‣ Peripheral blood smear ‣ Lactate dehydrogenase (LDH) ‣ Direct and indirect bilirubin ‣ Reticulocyte count ‣ Haptoglobin • Direct antiglobulin test (DAT) and cold agglutinin study if immune hemolysis is suspected • As clinically indicated: ‣ Bone marrow biopsy[b]/aspirate	**Hemolytic anemia[c]** →	ICI_HEM-2
		Aplastic anemia[d] →	ICI_HEM-3
		HLH-like syndrome[e,f] →	ICI_HEM-4
		Thrombocytopenia →	ICI_HEM-5

[a] Mild or transient Hb decreases or otherwise explained anemia may not require extensive workup. Consider the following factors when initiating assessment: baseline Hb, rapidity of change/timeline of assessment, persistence (≥2 weeks in separate tests), and severity.
[b] If aplastic anemia is suspected, a bone marrow biopsy is essential.
[c] Elevated LDH and low haptoglobin, elevated indirect bilirubin, microspherocytosis and/or red blood cell (RBC) agglutination on blood smear, DAT positivity. Note that a negative DAT alone does not rule out ICI-autoimmune hemolytic anemia.
[d] Anemia with or without leukopenia and thrombocytopenia. No evidence of nutrient deficiency (eg, B12), depressed reticulocytes.
[e] Findings may overlap with the traditional HLH diagnostic criteria (ie, HLH2004/HLH1994). Clinical findings may include: unexplained fever and hepatosplenomegaly. Laboratory findings may include: low counts, hypofibrinogenemia, elevated ferritin (≥500 ng/mL), elevated soluble IL-2 receptor levels (based on CD25), absent/low natural killer (NK) cell activity according to local laboratory reference, hypertriglyceridemia, and transaminitis. Histopathologic findings include: accumulation of lymphocytes/macrophages and hemophagocytosis; these may be identified via tissue biopsy, such as bone marrow, liver, or other tissues with suspected involvement (Henter JI, et al. Pediatr Blood Cancer 2007;48:124-131).
[f] ICI therapy can cause an HLH-like hyperinflammatory syndrome that may not meet the traditional diagnostic criteria for HLH. It is still unclear how the diagnosis and management of ICI-related HLH-like syndrome differ from immune effector cell (IEC)-associated HLH-like syndrome (IEC-HS) observed after chimeric antigen receptor (CAR) T-cell therapy. For IEC-HS diagnosis and management recommendations, see CART-2 in the NCCN Guidelines for Management of CAR T-Cell Therapy and Lymphocyte Engager-Related Toxicities.

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

HEMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT	GRADING	MANAGEMENT
Hemolytic anemia[c]	• See Assessment on ICI_HEM-1 • Increased monitoring of CBC and hemolysis labs • Evaluate for and rule out other non-ICI–related etiologies of hemolytic anemia ‣ Examples include viruses, bacteria, use of certain drugs [examples include dapsone], methemoglobinemia, bone marrow failure syndrome, or insect or reptile bites	Grade 1: Only laboratory evidence of hemolysis	• Hold immunotherapy[g] • Consider hematology referral
		Grade 2: Evidence of hemolysis and ≥2 g drop in Hb requiring monitoring only (without transfusion)	• Hold immunotherapy[g] • Prednisone 1 mg/kg once daily[h] • Consider hematology referral
		Grade 3: Hemolysis necessitating transfusion	• Discontinue immunotherapy[g] • Urgent hematology referral • Consider inpatient care • Blood transfusion per institutional guidelines • Prednisone/IV methylprednisolone 1 mg/kg once daily[h] • If no response to steroids after 5–7 days, consider adding rituximab ‣ If no response to steroids and rituximab, consider IVIG,[i] tacrolimus, cyclophosphamide, or mycophenolate mofetil
		Grade 4: Hemolysis and life-threatening consequences requiring urgent intervention	• Discontinue immunotherapy[g] • Inpatient care required with hematology consult • Blood transfusion per institutional guidelines • IV methylprednisolone 1 mg/kg once daily[h] • If no response to steroids after 3–5 days, consider adding rituximab ‣ If no response to steroids and rituximab, consider IVIG,[i] tacrolimus, cyclophosphamide, mycophenolate mofetil, or cyclosporine

Footnotes on ICI_HEM-2A

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

FOOTNOTES

[c] Elevated LDH and low haptoglobin, elevated indirect bilirubin, microspherocytosis and/or RBC agglutination on blood smear, DAT positivity. Note that a negative DAT alone does not rule out ICI-autoimmune hemolytic anemia.
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] Treat until Hb level is stable without transfusion then taper over 4 to 8 weeks.
[i] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.

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

HEMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT	GRADING	MANAGEMENT
Aplastic anemia[d] • Bone marrow cellularity <25% without an alternative etiology	• See Assessment on ICI_HEM-1 • Increased CBC monitoring • Paroxysmal nocturnal hemoglobinuria (PNH) • Evaluate for and rule out other non-ICI–related etiologies of aplastic anemia ‣ Examples include radiation exposure, certain toxins, viruses, infections, or prior treatments	Non-severe: Does not meet criteria for severe or very severe[j]	• Hold immunotherapy[g] • Consider: ‣ Red blood cell (RBC) and/or platelet transfusion as per institutional guidelines ‣ Hematology referral
		Severe[j] or Very severe[j]	• Discontinue immunotherapy[g] • Consider inpatient care with hematology consult ‣ RBC and/or platelet transfusion per institutional guidelines ‣ Consider growth factor support (eg, thrombopoietin mimetics, granulocyte colony-stimulating factor [G-CSF])[k] • Prednisone/IV methylprednisolone 1–2 mg/kg once daily[l] • If no response to steroids after 7 days: ‣ Consider IVIG,[i] cyclosporine, ATG, mycophenolate mofetil, or tacrolimus • Consider human leukocyte antigen (HLA) typing and evaluation for HCT if unresponsive to other therapies

[d] Anemia with or without leukopenia and thrombocytopenia. No evidence of nutrient deficiency (eg, B12), depressed reticulocytes.
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[j] Severe aplastic anemia must meet two of the following criteria: absolute reticulocyte count <50–60 x 10^9/L, platelet count <20 x 10^9/L, and/or absolute neutrophil count (ANC) <0.5 x 10^9/L. Very severe aplastic anemia must meet the same criteria as severe with the exception of an ANC of <0.2 x 10^9/L.
[k] NCCN Guidelines for Hematopoietic Growth Factors.
[l] Treat until symptoms improve to non-severe aplastic anemia, then taper over 4 to 8 weeks.

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

HEMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT	GRADING	MANAGEMENT
HLH-like syndrome[e,f,m] **Differential/suspect in settings of pancytopenia** • May overlap with hyperinflammatory syndromes such as cytokine release syndrome (CRS)[n] →	• See Assessment on ICI_HEM-1 • Additional laboratory tests: ferritin, fibrinogen, soluble IL-2 receptor (based on CD25), triglycerides • HScore[o] • Consider natural killer (NK) cell activity assessment per institutional guidelines • Evaluate for and rule out other non-ICI–related etiologies of HLH (eg, infection, lymphoma) →	No agreed upon grading scale; individual abnormalities may be graded (anemia, thrombocytopenia, fever, liver enzymes) →	• Hold immunotherapy[g] • Inpatient care[p] with hematology consult (due to high mortality rate if left untreated) ‣ Consider consult with expert in the management of HLH-like syndromes • Prednisone/IV methylprednisolone 0.5–1 mg/kg once daily[q] (or dexamethasone at equivalent dose)[q,r] • If no response to steroids after 5 days, consider adding tocilizumab,[s,t] anakinra, ruxolitinib, cyclosporine, or emapalumab-lzsg

[e] Findings may overlap with the traditional HLH diagnostic criteria (ie, HLH2004/HLH1994). Clinical findings may include: unexplained fever and hepatosplenomegaly. Laboratory findings may include: low counts, hypofibrinogenemia, elevated ferritin (≥500 ng/mL), elevated soluble IL-2 receptor levels (based on CD25), absent/low NK cell activity according to local laboratory reference, hypertriglyceridemia, and transaminitis. Histopathologic findings include: accumulation of lymphocytes/macrophages and hemophagocytosis; these may be identified via tissue biopsy, such as bone marrow, liver, or other tissues with suspected involvement (Henter JI, et al. Pediatr Blood Cancer 2007;48:124-131).
[f] ICI therapy can cause an HLH-like hyperinflammatory syndrome that may not meet the traditional diagnostic criteria for HLH. It is still unclear how the diagnosis and management of ICI-related HLH-like syndrome differ from IEC-HS observed after CAR T-cell therapy. For IEC-HS diagnosis and management recommendations, see CART-2 in the NCCN Guidelines for Management of CAR T-Cell Therapy and Lymphocyte Engager-Related Toxicities.
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[m] Noseda R, et al. J Immunother Cancer 2019;7:117.
[n] Liu LL, et al. J Immunother Cancer 2023;11:e005841.
[o] HLH2004 criteria were developed for pediatric populations. The HScore has been validated in adult populations and for reactive HLH in patients not treated with ICI. Its role in diagnosis of ICI-related HLH is unclear. Fardet L, et al. Arthritis Rheumatol 2014;66:2613-2620.
[p] Inpatient care is recommended for most, unless an expedited workup is possible. Inpatient care is required if ICI-related HLH-like syndrome is severe or life-threatening.
[q] Taper slowly (eg, up to 10 mg/week for prednisone/IV methylprednisolone or dexamethasone) and titrate for response with ongoing assessments for HLH flare (eg, monitoring inflammatory markers, ferritin).
[r] For dexamethasone dosing, see Hines MR, et al. Transplant Cell Ther 2023;29:438.e1-438.e16.
[s] Özdemir BC, et al. Ann Oncol 2020;12:1775-1778.
[t] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.

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

HEMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT	GRADING	MANAGEMENT[u]
Thrombocytopenia: platelet count < lower limit of normal (LLN) or relative decrease >50% from baseline	• Consider increased CBC monitoring • Peripheral blood smear • Reticulocyte count • PT/INR, partial thromboplastin time (PTT), fibrinogen • Abdominal ultrasound • Infection panel: HIV, hepatitis C virus (HCV), *H. pylori* • Consider bone marrow aspirate/biopsy if other test results are not conclusive or other cell lines affected and aplastic anemia suspected • Evaluate for and rule out other non-ICI–related etiologies of thrombocytopenia ‣ Examples include medication-related causes, infection, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and HLH	Grade 1 <LLN–75,000/mm³	• Continue immunotherapy • Monitor for signs of bleeding
		Grade 2 75,000/mm³–50,000/mm³	• Hold immunotherapy[g] • If no improvement within 4–6 weeks, consider prednisone/IV methylprednisolone 1 mg/kg once daily for 2–4 weeks, then taper over 4–6 weeks to lowest effective dose ‣ Consider adding IVIG[i] if bleeding • Consider hematology referral
		Grade 3 50,000/mm³–25,000/mm³ or Grade 4 <25,000/mm³	• Hold immunotherapy[g] • Hematology referral • Consider inpatient care • Prednisone/IV methylprednisolone 1–2 mg/kg once daily ‣ Consider adding IVIG[i] if bleeding • If no response to steroids after 1–2 weeks, consider rituximab or thrombopoietin receptor agonists (eg, romiplostim, eltrombopag)

[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[u] Thrombocytopenia induced by ICI is usually mild, may resolve spontaneously, and appears to respond to standard treatment algorithms for immune-related thrombocytopenia. Thus, standard institutional protocols may be appropriate for management.

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

MUSCULOSKELETAL ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[g]	
Inflammatory arthritis[a,b] →	• Number of joints involved • Consider arthrocentesis (cell count, gram stain and culture, crystal) analysis • Functional assessment • Consider joint ultrasound, or joint MRI with or without contrast if diagnosis of synovitis is unclear • Consider joint x-ray to rule out other causes • Disease markers (Anti-cyclic citrullinated peptide [anti-CCP] and rheumatoid factor [RF]) • Disease activity (CRP ± ESR) • Consider other forms of inflammatory arthritis[c]	Mild[d] →	• Continue immunotherapy if active measure below effective; otherwise hold immunotherapy[h] • NSAIDs[i] ▸ If NSAIDs ineffective, consider prednisone 10–20 mg/day; if unable to taper after 1 week, hold immunotherapy[h] (if not already done) and increase prednisone to 30 mg/day[j,k] ▸ If unable to taper prednisone from 30 mg/day after 1 week, consider initiating conventional synthetic disease-modifying antirheumatic drug (csDMARD)[l,m] • Consider rheumatology consultation[n]	→ Monitor with serial rheumatologic examinations ± ESR, CRP every 4–8 weeks after treatment[t]
		Moderate[e] →	• Consider holding immunotherapy[h] • Rheumatology consultation[n] • Prednisone 10–20 mg/day[j] ▸ If unable to taper after 1 week, hold immunotherapy[h] (if not already done), increase prednisone to 30 mg/day[j,k] ▸ If unable to taper prednisone from 30 mg/day after 1 week, consider initiating csDMARD,[l,m,o] IL-6 inhibitors[l] (tocilizumab or sarilumab),[p] or tumor necrosis factor (TNF) inhibitors[l,q,r]	
		Severe[f] →	• Hold immunotherapy[h,s] • Rheumatology consultation[n] • Prednisone 20–30 mg/day[j,k] ▸ If unable to taper after 1 week, consider initiating csDMARD,[l,m,o] IL-6 inhibitors[l] (tocilizumab or sarilumab),[p] or TNF inhibitors[l,q,r]	

Footnotes on ICI_MS-1A

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

FOOTNOTES

[a] Signs of inflammation include: joint swelling, morning stiffness (>1 hour), stiffness after inactivity, improvement in stiffness with activity, elevated CRP and/or ESR, or signs of synovitis on imaging.
[b] ICI IA can be seen with PMR-like manifestations.
[c] Such as gout, infection, or pseudogout.
[d] Mild in severity; only 1 or 2 joints involved. Consider aspiration to rule out septic joint if infection is suspected.
[e] At least one joint with severe inflammation.
[f] Limits ADLs, several joints involved.
[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Consider other non-opioid medications (eg, COX2 inhibitors or gabapentin/pregabalin).
[j] Treat until symptoms improve to mild, then taper over 4–6 weeks.
[k] If patients need to be on steroids long-term, see IMMUNO-A.
[l] Perform the following screening tests prior to initiation of DMARDs: hepatitis serologies, CBC, TB, and liver tests.
[m] csDMARDs include: methotrexate 15–20 mg (PO or SQ) every 7 days with folic acid 1 mg/day to reduce side effects. If methotrexate is contraindicated (including but not limited to: renal dysfunction, hepatic dysfunction, etc.), consider sulfasalazine starting at 500 mg PO BID (contraindicated in those with a sulfa allergy and requires assessment of glucose-6-phosphate dehydrogenase (G6PD) level prior to starting), leflunomide 10–20 mg/day PO, or hydroxychloroquine 200 mg PO daily or BID based on weight (contraindicated in those with retinopathy).
[n] Consider intra-articular steroids in affected joint(s), depending on joint location and number involved and joint aspiration and fluid analysis.
[o] For patients with significant concomitant inflammatory axial (spine and sacroiliac joint) inflammatory symptoms, TNF inhibitors should be preferred over csDMARDs.
[p] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab or sarilumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.
[q] TNF inhibitors include etanercept, adalimumab, infliximab, golimumab, or certolizumab. There is a slight increased risk of relapse.
[r] In inflammatory arthropathies that have symptoms suggestive of psoriatic arthritis or spondyloarthropathies, consider agents that are approved for these indications such as apremilast, IL-17, IL-12, or IL-23 inhibitors.
[s] Consider discontinuing immunotherapy if arthritis worsens, with repeated dosing, to the point where daily activities are limited or patient's quality of life is severely impaired.
[t] Consider ESR and CRP to monitor response if elevated at the onset of therapy. Inflammatory arthritis may become a chronic process requiring long-term management.

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

MUSCULOSKELETAL ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[g]
Polymyalgia rheumatica (PMR)[u,v]	• Assess for bilateral shoulder and hip girdle pain, and morning stiffness • Screen for GCA symptoms (see below) ▸ If visual symptoms or loss, see GCA Assessment/Grading and Management below • ESR and CRP	• Continue immunotherapy ▸ If vision changes or loss present, hold immunotherapy until evaluated for GCA[h] • Start prednisone 10–20 mg/day with slow taper over 6–8 weeks[w] ▸ If no resolution, consider holding immunotherapy[h] and increasing prednisone to 30–40 mg[x] ▸ If unable to taper prednisone or no improvement in symptoms, consider: ◊ csDMARDs such as methotrexate ◊ IL-6 inhibitors (tocilizumab or sarilumab)[p] ▸ Rheumatology consultation
Giant cell arteritis (GCA) (visual symptoms, headache, scalp tenderness, jaw claudication, often associated with fevers, night sweats, and weight loss)	• Screen for GCA symptoms ▸ If symptoms present, initiate prednisone 1 mg/kg/day with urgent referral to vascular surgery or ophthalmology for temporal artery biopsy ± ultrasound due to risk of vision loss ▸ If available, refer to rheumatology • ESR and CRP	• Hold immunotherapy[h] • If not already started, initiate prednisone 1 mg/kg/day taper over 8–12 weeks,[x,y] longer taper may be required • Urgent referral to rheumatology even in mild cases for consideration of IL-6 inhibitors (tocilizumab or sarilumab)[p] • If visual symptoms: ▸ Consider IV methylprednisolone 500–1000 mg x 3 days, followed by prednisone 1 mg/kg, then taper[x,y] ▸ Urgent referral to ophthalmology or vascular surgery

[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab or sarilumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.
[u] Pain and/or stiffness in the morning usually involving bilateral shoulders and hip girdle region that limits instrumental or self-care ADLs.
[v] ICI PMR can be seen with peripheral arthritis.
[w] If improving in 4 weeks, taper by 2.5 mg every 2–4 weeks.
[x] *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis if it is anticipated that patient will be treated with >20 mg prednisone for >4 weeks.
[y] GCA requires a slower taper. Goldstein BL, et al. Arthritis Rheumatol 2014;66:768-769; Micaily I, et al. Ann Oncol 2017;28:2621-2622; Calabrese LH, et al. Nat Rev Rheumatol 2018;14:569-579.

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

MUSCULOSKELETAL ADVERSE EVENT(S) → **ASSESSMENT/GRADING** → **MANAGEMENT[g]**

Myositis[z] (proximal muscle weakness, neck flexor weakness, dysphagia, with or without myalgias)

Assessment:
- Evaluate for concomitant irAEs myasthenia gravis/ myasthenia gravis-like syndrome and myocarditis, as myositis can exist as an overlap syndrome[aa,bb]
- Urgent evaluation is essential with labs and clinical team
- CK, aldolase, and troponin I or T levels, CMP (AST/ ALT may be elevated in myositis), ECG (compare to baseline if possible)
- Muscle strength testing (proximal muscles, including neck flexors, and distal muscles)
- Consider MRI without contrast, electromyography (EMG), muscle biopsy, and myositis antibodies if clinically indicated

Mild[cc] or Moderate[dd] →
- Consider holding or discontinuing immunotherapy[h,ff]
- Prednisone 0.5–1 mg/kg[gg,hh]
- Monitor serial CK/aldolase[ii]
- If no response to therapy, consider re-evaluating for myasthenia gravis/myasthenia gravis-like syndrome (ICI_NEURO-1) and myocarditis (ICI_CARDIO-1), and escalate to management for severe or life-threatening myositis[jj]

Severe or Life-threatening[ee] →
- Hold immunotherapy; consider permanent discontinuation in select patients[h]
- Inpatient care for severe or life-threatening myositis
- Rheumatology or neurology consultation
  - Cardiology and/or neurology consultation if myocarditis and/or myasthenia gravis/myasthenia gravis-like syndrome is involved[jj]
- Consider IV methylprednisolone 500 mg to 1 g/day x 3 days followed by prednisone 1 mg/kg/day. After 4 weeks, taper prednisone by 10 mg every 2 weeks to 0.5 mg/kg/day and then 10 mg/month as clinical status allows
  - If no improvement after 2–4 weeks, consider the addition of a csDMARD[hh]
- If significant dysphagia, life-threatening situations, or refractory to steroids with minimal improvement after 1 week, consider IVIG[kk], methotrexate,[ll] mycophenolate mofetil, or rituximab
  - Abatacept with ruxolitinib has been used in concomitant myositis and myocarditis[mm]
- Monitor serial aldolase/CK until symptoms have resolved and tapered off steroids

Footnotes on ICI_MS-3A

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

FOOTNOTES

[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[z] Myositis is a disorder characterized by inflammation and/or weakness involving the skeletal muscles with elevated muscle enzymes.
[aa] Myocarditis symptoms are nonspecific (eg, chest pain, dyspnea, fatigue, palpitations [arrhythmia: heart block or ventricular ectopic beats], syncope, generalized weakness) and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis/myasthenia gravis-like syndrome (3 M's), and more common with combination therapy. In most fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.
[bb] These concomitant irAEs can occur within the first month of therapy (median onset of 28–30 days).
[cc] CK elevation <1000 mcg/L, mild weakness, and minimal impairment of ADLs; no myasthenia gravis/myasthenia gravis-like syndrome and/or myocarditis coexisting with myositis.
[dd] Moderate pain associated with objective weakness and/or elevation of muscle enzymes (CK or aldolase) limiting self-care ADLs.
[ee] Urgent intervention is indicated.
[ff] Would not recommend holding ICI if no elevation in CK or evidence of active myositis.
[gg] If improving after 2–4 weeks, begin slow prednisone taper by 5 mg/week. If unable to taper, or no response, add csDMARD.
[hh] Methotrexate (with folic acid) as a steroid-sparing agent to speed up taper. If contraindication to methotrexate, consider mycophenolate mofetil or azathioprine.
[ii] Do not need to trend aldolase unless aldolase elevation is the only evidence of myositis (CK normal). Aldolase can be falsely elevated if blood sample is hemolyzed.
[jj] There have been case reports of a life-threatening triad of myositis, myocarditis, and myasthenia gravis/myasthenia gravis-like syndrome.
[kk] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[ll] Methotrexate 15–25 mg weekly by oral or subcutaneous route.
[mm] Salem JE, et al. Cancer Discov 2023;13:1100-1115.

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

NERVOUS SYSTEM ADVERSE EVENT(S)

Myasthenia gravis/myasthenia gravis-like syndrome[a]

ASSESSMENT/GRADING

- Evaluate for concomitant irAEs myocarditis (ICI_CARDIO-1) and myositis (ICI_MS-3) as myasthenia gravis/myasthenia gravis-like syndrome can exist as an overlap syndrome[b]
  - Cardiac exam and ECG
  - Troponin, CK, and aldolase
  - Consider transthoracic echocardiogram (TTE)
- Neurology consultation
- AChR antibodies, anti–muscle-specific tyrosine kinase antibodies, and anti-striational antibodies in blood (not needed for diagnosis)
- Pulmonary function assessment with negative inspiratory force (NIF) and vital capacity (VC)
- EMG/nerve conduction study (NCS) with repetitive nerve stimulation and, if available, single-fiber EMG
- Consider MRI of the brain with and without contrast to rule out metastasis/leptomeningeal disease if there is facial/ocular/bulbar weakness

MANAGEMENT[e]

Moderate (G2)[c] →
- Discontinue immunotherapy[f]
- Consider inpatient care (even for initially mild cases, which can progress rapidly with a high mortality rate)
- Low-dose oral prednisone 20 mg daily[g]
  - If no symptom improvement on low dose
    - ◊ Increase every 3–5 days to a target dose of 1 mg/kg/day but not >100 mg daily
    - ◊ Taper steroid based on symptom improvement
- Pyridostigmine 30 mg 3 times a day and gradually increase to maximum of 120 mg orally 4 times a day as tolerated and based on symptoms

Severe (G3–4)[d] →
- Permanently discontinue immunotherapy[f]
- Inpatient care (may need ICU-level monitoring)
- IV methylprednisolone 1–2 mg/kg/day[g] (steroid taper based on symptom improvement)
- Initiate plasmapheresis or IVIG[h]
  - Consider adding rituximab (375 mg/m² weekly for 4 treatments or 500 mg/m² every 2 weeks for 2 doses) if refractory to plasmapheresis or IVIG
- Frequent pulmonary function assessment
- Daily neurologic evaluation
- Avoid medications that can worsen myasthenia[g,i]

[a] Progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (ie, ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis and myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller Fisher variant of GBS has overlapping symptoms (ophthalmoplegia and ascending weakness).
[b] Myocarditis symptoms are nonspecific (eg, chest pain, dyspnea, fatigue, palpitations [arrhythmia: heart block or ventricular ectopic beats], syncope, generalized weakness) and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis/myasthenia gravis-like syndrome (3 M's), and more common with combination therapy. In most fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.
[c] Some symptoms interfering with ADLs. Myasthenia Gravis Foundation of America (MGFA) severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).
[d] 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–IV moderate to severe generalized weakness to myasthenic crisis.
[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] High-dose steroids (≥2 mg/kg/day) may exacerbate symptoms.
[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[i] Examples include, but are not limited to, beta-blockers, fluoroquinolones, and IV magnesium.

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

NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[e]
Guillain-Barré syndrome (GBS)[j] →	• Inpatient care with access to ICU-level monitoring • Neurology consultation • MRI of the spine with and without contrast (rule out compressive lesion) • Serum ganglioside antibody tests for GBS variants (GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia) • PFTs (NIF/VC) • EMG/NCS[k] • Lumbar puncture[l] (to exclude leptomeningeal disease, which can mimic GBS) →	Moderate (G2)[m] or Severe (G3–4)[n] →	• Discontinue immunotherapy[f] • Inpatient care with capability of rapid transfer to ICU-level monitoring • Start IVIG[h] or plasmapheresis in addition to IV methylprednisolone 1 gram daily for 5 days[o] then taper over 4 weeks • Frequent neurologic evaluation and pulmonary function monitoring • Monitor for concurrent autonomic dysfunction • Gabapentin, pregabalin, or duloxetine for pain

[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[j] Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in lower back and thighs.
[k] Early EMG/NCS findings may assess potential severity of GBS (Sejvar JJ, et al. Vaccine 2011;29:599-612; Leonhard SE, et al. Nat Rev Neurol 2019;15:671-683) and rule out sensory ganglionopathy, which may have a different prognosis.
[l] Cerebrospinal fluid (CSF) typically has elevated protein and often elevated white blood cell (WBC) count; while cytology is negative in typical GBS, it is important to send given the risk of leptomeningeal carcinomatosis. Consider ID consult. ID workup: Measure opening pressure and check cell count, protein glucose, Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion and cytology. May see normal glucose, normal culture, and Gram stain. May see reactive lymphocytes or histiocytes on cytology.
[m] Some interference with ADLs, symptoms concerning to patient.
[n] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[o] Steroids are not usually recommended for idiopathic GBS; however, in immunotherapy-related forms, a trial is reasonable in addition to IVIG or plasmapheresis.

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

NERVOUS SYSTEM ADVERSE EVENT(S)	GRADING	ASSESSMENT	MANAGEMENT[e]
Peripheral neuropathy[p,q]	Mild (G1)[r] and Moderate (G2)[s] →	• Evaluate for other causes of neuropathy such as: chemotherapy, other medications, infection, metabolic/endocrine disorders, environmental exposures, vascular or autoimmune disease, trauma, etc. →	See Management for Mild (G1) or Moderate (G2)
	Mild (G1)[r] →	• Consider B12, HbA1c, serum protein electrophoresis (SPEP) with immunofixation, HIV, and antineutrophil cytoplasmic antibody (ANCA) • Consider neuraxial imaging as per neurology →	• Consider holding immunotherapy[f,u] • Monitor symptoms for a week[v]
	Moderate (G2)[s] →	• B12, HbA1c, SPEP with immunofixation, HIV, and ANCA • Neuraxial imaging as per neurology • Consider EMG/NCS • Consider neurology consultation →	• Hold immunotherapy[f] • Initial observation or initiate prednisone 0.5–1 mg/kg orally (if progressing from mild)[w] • If progression, initiate IV methylprednisolone 2–4 mg/kg/day[w] and see GBS (ICI_NEURO-2) • Gabapentin, pregabalin, or duloxetine for pain
	Severe (G3–4)[t] →	GBS (ICI_NEURO-2)	

[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] The presence of painful, asymmetric sensory/motor deficits should raise concern for mononeuritis multiplex and prompt evaluation for vasculitis or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit.
[q] GI tract paresis due to myenteric neuritis is a rare toxicity associated with ICI therapy. The presentation may be fulminant with profound ileus. Early institution of high-dose steroids in concert with multidisciplinary management is recommended.
[r] No interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate.
[s] Some interference with ADLs, symptoms concerning to the patient (ie, pain but no weakness or gait limitation).
[t] Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes). Severe peripheral neuropathy and sensory ganglionopathy are not necessarily GBS but the management can be similar.
[u] There is a low threshold to hold ICIs in mild cases of peripheral neuropathy.
[v] Specifically monitor for new interference with iADLs from either pain or weakness, gait difficulty, ataxia, or autonomic changes.
[w] Treat until symptoms improve to grade ≤1, then taper over 4–6 weeks.

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

NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[e]
Aseptic meningitis[x] →	• MRI of the brain with and without contrast[z] + pituitary protocol • Consider MRI of the spine with and without contrast, especially if abnormal neurologic exam of extremities, or unable to obtain exam • Lumbar puncture (to exclude leptomeningeal disease)[aa] • Consider neurology consultation	→ • Hold immunotherapy[f] if mild/moderate • Consider discontinuing immunotherapy if severe • Inpatient care (G3–4[cc]) • Consider IV acyclovir[dd] until HSV and varicella zoster virus (VZV) PCR results obtained • Add bacterial coverage until cultures/panel results are back • Rule out bacterial and viral infection, then closely monitor off steroids • Start prednisone 0.5–1 mg/kg/day. For severe symptoms may start IV methylprednisolone 1–2 mg/kg/day[ee]
Encephalitis[y] →	• Neurology consultation • MRI of the brain with and without contrast[bb] • Consider MRI of the spine with and without contrast, especially if abnormal neurologic exam of extremities, or unable to obtain exam • Lumbar puncture[aa] • Electroencephalogram (EEG) to evaluate for non-convulsive seizure • ESR, CRP, ANCA (if vasculitic process suspected) • Autoimmune encephalopathy in cerebrospinal fluid (CSF) and serum	→ • Hold immunotherapy[f] if mild • Discontinue immunotherapy if moderate/severe • Inpatient care (G3–4[cc]) • Consider IV acyclovir[dd] until HSV and VZV PCR results are obtained • Add bacterial coverage until cultures/panel results are back; manage in consultation with ID team • Trial of IV methylprednisolone 1–2 mg/kg/day[ee] • If severe or progressing symptoms over 24 h, strongly consider IV methylprednisolone 1 g daily for 3–5 days plus IVIG[h] or plasmapheresis • If positive for autoimmune encephalopathy antibody or limited or no improvement after 7–14 days, consider rituximab

[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[x] May present with headache, photophobia, and neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
[y] Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality.
[z] May reveal leptomeningeal enhancement that can resemble leptomeningeal metastasis. CSF sampling for cytology evaluation is needed to differentiate.
[aa] Measure opening pressure and check cell count, protein glucose, Gram stain, culture, PCR for HSV, VZV, CMV, and other viral PCRs depending on suspicion, cytology, flow cytometry, and oligoclonal bands. If the patient is encephalopathic, check autoimmune encephalopathy panel. May see elevated WBC with normal glucose, normal culture, Gram stain, and elevated protein. May see reactive lymphocytes or histiocytes on cytology.
[bb] May reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
[cc] Limiting self-care and aids warranted.
[dd] 10 mg/kg IV every 8 hours.
[ee] Taper steroids over 4 weeks once symptoms resolve.

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

NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[e]
Demyelinating disease[ff] (optic neuritis,[gg] transverse myelitis,[hh] ADEM[ii] [acute demyelinating encephalomyelitis]) →	• **Neurology consultation** • **MRI of the spine and brain with and without contrast[jj]** • **Lumbar puncture[kk]** • **B_{12}, copper, HIV, syphilis serologies, antinuclear antibody (ANA), anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, autoimmune encephalopathy panel, and paraneoplastic panel** • **Evaluation for constipation and urinary retention with bladder scan** →	• **Discontinue immunotherapy[f]** • **Inpatient care** • **IV methylprednisolone 1 g/day[ee] for 3–5 days** • **If there is no response or worsening after 48 hours on high-dose IV methylprednisolone, consider IVIG[h] or plasmapheresis** • **For management of optic neuritis, see ICI_OCUL-3**

[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[ee] Taper steroids over 4 weeks once symptoms resolve.
[ff] Guidon AC, et al. J Immunother Cancer 2021;9:e0028890.
[gg] Vision loss, eye pain, decreased visual acuity, visual field loss, dyschromatopsia, relative afferent pupillary defect, optic disc edema.
[hh] Acute or subacute weakness or sensory changes bilaterally, often with bowel/bladder changes and spinal level to pinprick, hyperreflexia, positive Babinski.
[ii] May present with headache, confusion, seizures, depressed level of consciousness, speech abnormality, focal weakness, sensory change (numbness or tingling), ataxia/loss of balance, or vision loss.
[jj] In patients with suspected optic neuritis, MRI of the orbits with and without contrast is recommended.
[kk] Cell count, protein, glucose, oligoclonal bands, viral PCRs, flow cytometry and cytology, and paraneoplastic panel.

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

OCULAR ADVERSE EVENT(S) | **ASSESSMENT/GRADING** | **MANAGEMENT BASED ON COLLABORATION WITH OPHTHALMOLOGY[d]**

Vision or ocular changes[a,b] →

- Ophthalmology evaluation and management essential with vision testing to include:
  - Visual acuity in each eye
  - Color vision
  - Pupil size, shape, and reactivity
  - Visual field
  - Intraocular pressure (IOP)
  - Retinal nerve fiber layer (RNFL)
  - Macula optical coherence tomography (OCT)
  - Dilated fundoscopic examination
  - Slit lamp examination
- Evaluate for other common causes (HLA-B27), including ID[c]

Uveitis

- Anterior or intermediate uveitis (G1 or G2) →
  - G1: Continue immunotherapy and monitor
  - G2: Hold immunotherapy to observe for worsening uveitis; if uveitis is stable on topical therapy, consider restarting immunotherapy in discussion with ophthalmology[e]
  - Treatment guided by ophthalmology to include ophthalmic prednisolone ± systemic prednisone/IV methylprednisolone[f,g]
- Posterior or panuveitis (G3); 20/200 or worse vision (G4) →
  - Hold immunotherapy[e]
  - Treatment guided by ophthalmology to include ophthalmic prednisolone and systemic prednisone/IV methylprednisolone[f,g]

Episcleritis

- Mild (G1) →
  - Continue immunotherapy
  - Artificial tears
- Moderate decrease (worse than 20/20 but better than 20/40, or ≤3 lines decreased vision from baseline) (G2); Marked decrease (worse than 20/40 or >3 lines of decreased vision from baseline, up to 20/200) (G3); 20/200 or worse vision (G4) →
  - Hold immunotherapy[e]
  - Treatment guided by ophthalmology to include ophthalmic NSAID or prednisolone or systemic prednisone/IV methylprednisolone[f]

See ICI_OCUL-2 for scleritis, keratitis, or maculopathy; ICI_OCUL-3 for blepharitis, orbital myositis/thyroid-like eye disease/cranial neuropathy, optic neuritis/neuropathy

Footnotes on ICI_OCUL-3A

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

OCULAR ADVERSE EVENT(S)

Vision or ocular changes[a,b]

ASSESSMENT/GRADING

- Ophthalmology evaluation and management essential with vision testing to include:
  - Visual acuity in each eye
  - Color vision
  - Pupil size, shape, and reactivity
  - Visual field
  - IOP
  - RNFL
  - Macula OCT
  - Dilated fundoscopic examination
  - Slit lamp examination
- Evaluate for other common causes (HLA-B27), including ID[c]

MANAGEMENT BASED ON COLLABORATION WITH OPHTHALMOLOGY[d]

Scleritis

- Mild (G1) → Oral NSAIDs (eg, flurbiprofen, indomethacin)
- Moderate decrease (worse than 20/20 but better than 20/40, or ≤3 lines decreased vision from baseline) (G2)
- Marked decrease (worse than 20/40 or >3 lines of decreased vision from baseline, up to 20/200) (G3)
- 20/200 or worse vision (G4)
  → • Hold immunotherapy[e]
  • Treatment guided by ophthalmology to include systemic prednisone/IV methylprednisolone[g]

Keratitis

- Mild (G1) → • Continue immunotherapy • Artificial tears
- Moderate decrease (worse than 20/20 but better than 20/40, or ≤3 lines decreased vision from baseline) (G2)
  → • Continue immunotherapy
  • Topical drops (eg, cyclosporine ophthalmic drops 0.05%, prednisolone ophthalmic drops)
- Marked decrease (worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200) (G3)
- 20/200 or worse vision or corneal perforation (G4)
  → • Hold immunotherapy[e]
  • Treatment guided by ophthalmology to include topical drops (eg, cyclosporine ophthalmic drops 0.05%, prednisolone ophthalmic drops), serum tears, or scleral lenses

Maculopathy

- Mild (G1)
- Moderate decrease (worse than 20/20 but better than 20/40, or ≤3 lines decreased vision from baseline) (G2)
- Marked decrease (worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200) (G3)
- 20/200 or worse vision (G4)
  → • Hold immunotherapy[e]
  • Treatment guided by ophthalmology to include ophthalmic prednisolone or systemic prednisone/IV methylprednisolone[f]

Footnotes on ICI_OCUL-3A

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

OCULAR ADVERSE EVENT(S)

Vision or ocular changes[a,b] →

ASSESSMENT

- Ophthalmology evaluation and management essential with vision testing to include:
  - Visual acuity in each eye
  - Color vision
  - Pupil size, shape, and reactivity
  - Visual field
  - IOP
  - RNFL
  - Macula OCT
  - Dilated fundoscopic examination
  - Slit lamp examination
- Evaluate for other common causes (HLA-B27), including ID[c]

MANAGEMENT BASED ON COLLABORATION WITH OPHTHALMOLOGY[d]

Blepharitis

- Mild (G1)
- Moderate decrease (worse than 20/20 but better than 20/40, or ≤3 lines decreased vision from baseline) (G2)

→ • Continue immunotherapy
• Warm compresses and/or artificial tears

- Marked decrease (worse than 20/40 or >3 lines of decreased vision from baseline, up to 20/200) (G3)
- 20/200 or worse vision (G4)

→ • Hold immunotherapy[e]
• Treatment guided by ophthalmology to include oral doxycycline or topical antibiotic ointments

Orbital myositis/thyroid-like eye disease/cranial neuropathy →

- Mild (G1)
- Moderate decrease (worse than 20/20 but better than 20/40, or ≤3 lines decreased vision from baseline) (G2)
- Marked decrease (worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200) (G3)
- 20/200 or worse vision (G4)

→ • Hold immunotherapy[e]
• Treatment guided by ophthalmology to include systemic prednisone[f]

Optic neuritis/neuropathy →

- Mild (G1)
- Moderate decrease (worse than 20/20 but better than 20/40, or ≤3 lines decreased vision from baseline) (G2)
- Marked decrease (worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200) (G3)
- 20/200 or worse vision (G4)

→ • Hold immunotherapy[e]
• Treatment guided by ophthalmology to include systemic prednisone/IV methylprednisolone[f]

Footnotes on ICI_OCUL-3A

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

FOOTNOTES

[a] Patients experiencing ocular AEs may present with any of the following symptoms: blurred/distorted vision, blind spots, change in color vision, diplopia, photophobia, tenderness/pain, eyelid swelling, and proptosis. Both uveitis and episcleritis can be associated with eye redness but slit lamp examination is essential to rule out anterior chamber inflammation.
[b] See ICI_MS-2 for management of GCA.
[c] Etiologies such as syphilis, toxoplasmosis, and TB can cause uveitis and therefore should be evaluated for and ruled out prior to stopping ICI therapy and/or initiating other local therapies.
[d] Principles of Immunosuppression (IMMUNO-A).
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] Treat with 1 mg/kg/day, not to exceed 60 mg/day until symptoms improve to grade ≤1, then taper over 4–6 weeks.
[g] If refractory to high-dose systemic steroids, consider adding infliximab, or antimetabolites (eg, methotrexate) for panuveitis.

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

PULMONARY ADVERSE EVENT(S) | **GRADING** | **MANAGEMENT**[f]

Pneumonitis[a]

Mild (G1)[b] →
- Consider holding immunotherapy[g]
- Reassess in 1–2 weeks
  - History and physical (H&P)
  - Pulse oximetry (resting and with ambulation)
- Consider chest CT with contrast[h,i]
  - Consider repeat chest CT in 4–6 weeks or as clinically indicated if patient develops symptoms

Moderate (G2)[c,d] →
- Hold immunotherapy[g]
- Consider pulmonary consultation
- Minimally invasive evaluation
  - Consider infectious workup:
    - ◊ Nasal swab for potential viral pathogens[j]
    - ◊ Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (eg, *pneumococcus*, *legionella*)
  - Chest CT with contrast[h,i] and repeat chest CT in 3–4 weeks
- Invasive evaluation
  - Consider early bronchoscopy with BAL (send for institutional immunocompromised panel[k]) and consider transbronchial lung biopsy if clinically feasible to evaluate for progressive malignancy, fungal infections, or steroid responsive ILD
- Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
- Prednisone/IV methylprednisolone 1–2 mg/kg/day[l]
  - Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for steroid-dependent pneumonitis at the time of steroid tapering[m]
- Monitor every 3–7 days with[n]:
  - H&P and pulse oximetry (resting and with ambulation)
- If no improvement after 48–72 hours of steroids,[o] treat as grade 3

Severe (G3–4)[e] → ICI_PULM-2

Footnotes on ICI_PULM-2A

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

ASSESSMENT/ GRADING

Severe (G3–4)[e] pneumonitis[a] →

MANAGEMENT[f]

- Hold immunotherapy[g]
- Inpatient care
- Pulmonary and ID consultation
- Minimally invasive evaluation
  - Infectious workup:
  - Consider that the patient may be immunocompromised
    - ◊ Nasal swab for potential viral pathogens[j]
    - ◊ Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (eg, *pneumococcus*, *legionella*)
    - ◊ Consider cardiac evaluation to exclude cardiac causes for clinical presentation
- Invasive evaluation
  - Bronchoscopy with BAL (send for institutional immunocompromised panel[k]) if feasible to rule out infection, malignant lung infiltration, or steroid responsive ILD and consider transbronchial lung biopsy if feasible and clinically indicated
- Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
- IV methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks[f]
- Consider adding any of the following if no improvement after 48 hours:
  - Preferred:
    - ◊ IVIG[p]
    - ◊ Tocilizumab[q]
  - Other recommended:
    - ◊ Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service[m]
      - – Consider mycophenolate mofetil as a steroid-sparing immunosuppressant for steroid-dependent pneumonitis at the time of steroid tapering[m]
    - ◊ Infliximab[r] 5 mg/kg, a second dose may be repeated 14 days later at the discretion of the treating provider

Footnotes on ICI_PULM-2A

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

FOOTNOTES

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging). Symptoms may include dry cough, shortness of breath, fever, chest pain, and increased oxygen requirement. The imaging features of pneumonitis are known to be variable and may include ground-glass opacities, organizing pneumonia, hypersensitivity, reticulonodular changes, or a mixture of all these appearances.
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma.
[c] Presence of new/worsening symptoms.
[d] Consider cardiac etiologies.
[e] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs, oxygen indicated; G4–life-threatening respiratory compromise.
[f] Principles of Immunosuppression (IMMUNO-A).
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] CT with contrast to rule out other etiologies if not contraindicated.
[i] See Pre-Therapy Assessment: Pulmonary on IMMUNO-2.
[j] Viral pathogen assessment should include influenza, COVID-19, and respiratory syncytial virus (RSV).
[k] Immunocompromised panel may include CBC with differential, bacterial culture, and Gram stain; AFB culture and stain; fungal immunoassay, culture, and silver stain; and/or CMV, HSV, PJP, and respiratory virus PCR.
[l] Treat until symptoms improve to grade ≤1, then taper over 4–6 weeks.
[m] Mycophenolate mofetil is unlikely to improve steroid-unresponsive pneumonitis immediately but may have clinical benefit to avoid steroid dependence.
[n] If clinically indicated and appropriate, monitoring can be done with telemedicine.
[o] In people with pre-existing/underlying lung compromise, greater clinical suspicion and caution should be taken.
[p] IVIG 2 g/kg divided in equal doses given over 2–5 consecutive days. Refer to the FDA-approved package insert for important safety information.
[q] Khanna D, et al. Lancet 2016;387:2630-2640; Khanna D, et al. Lancet Respir Med 2020;8:963-974; Manfredi A, et al. Intern Med J 2020;50:1085-1090. Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.
[r] Data for infliximab demonstrate mixed response for treatment of ICI-pneumonitis and use of this agent should be considered carefully.

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

RENAL ADVERSE EVENT(S)	ASSESSMENT	GRADING	MANAGEMENT[i]
Elevated serum creatinine (sCR)/acute kidney injury (AKI)[a]	• Check BUN, spot urine protein/creatinine ratio, urine microalbumin/creatinine ratio, urine electrolytes (sodium, creatinine),[b] and urinalysis[c] • Evaluate potential alternative etiologies (recent IV contrast, medications, fluid status, urinary tract infection [UTI])[d] • Imaging to rule out acute obstructive uropathies • If there is new or worsening proteinuria, rule out acute glomerulonephritis[e]	General: Stage 1, 2, and 3 AKI	• Limit/discontinue nephrotoxic medications and dose adjust to creatinine clearance • Avoid PPIs; use H2 blockers for GI prophylaxis if initiating corticosteroids • Consider increased oral/IV hydration and reassess • Check sCR every 3–7 days
		Stage 1 AKI[f]	• Consider holding immunotherapy[j] • Consider nephrology consult if sustained elevations in creatinine
		Stage 2 AKI[g]	• Hold immunotherapy[j] • Nephrology consultation • Prednisone 0.5–1 mg/kg/day[k] • Consider renal biopsy[l] if no improvement within 5–7 days and/or new proteinuria • For persistent stage 2 beyond 1 week, prednisone/IV methylprednisolone 1–2 mg/kg/day[k]
		Stage 3 AKI[h]	• Hold immunotherapy[j] • Consider inpatient care • Nephrology consultation • Prednisone/IV methylprednisolone 1–2 mg/kg/day[k] • Renal biopsy[l] if no improvement within 5–7 days and/or new proteinuria • Based on biopsy results, consider adding one of the following if kidney injury remains >stage 2 after 4–6 weeks of steroids or if creatinine increases during steroid taper (or once off steroids) (in alphabetical order)[m]: ▸ Azathioprine ▸ Infliximab[n] ▸ Mycophenolate mofetil ▸ Rituximab

Footnotes on ICI_RENAL-1A

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

FOOTNOTES

[a] Azotemia, creatinine elevation, and inability to maintain acid/base or electrolyte balance.
[b] Rule out pre-renal volume depletion and/or acute tubular necrosis.
[c] Frequency and additional lab tests to be determined in consultation with nephrology to inform treatment.
[d] General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDs and PPIs, and consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.
[e] For proteinuria >1 g/24-hour with no other etiology for proteinuria present such as diabetes or hypertension and/or gross or microscopic hematuria, check ANA; RF; ANCA; anti-double-stranded DNA (dsDNA); serum C3, C4, and CH50; hepatitis B and C reflexive panels; SPEP; and urine protein electrophoresis (UPEP). For ICI-induced etiologies such as vasculitis and glomerulonephritis, check the following serologies, in addition to obtaining a kidney biopsy: ANA, dsDNA, RF, C3, C4, ANCA, anti-glomerular basement membrane (GBM), hepatitis B and C, HIV, rapid plasma reagin (RPR), SPEP, UPEP, and immunofixation electrophoresis (IFE). Consider 24-hour urine collection.
[f] 1.5 to <2x baseline or increase of ≥0.3 mg/dL over 48 hours.
[g] 2 to <3x baseline.
[h] ≥3.0x baseline; 4.0 mg/dL or need for renal replacement therapy (RRT); dialysis as indicated.
[i] Principles of Immunosuppression (IMMUNO-A).
[j] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k] Treat until symptoms improve to grade ≤1, then taper over 4–6 weeks. Gupta S, et al. J Immunother Cancer 2022;10:e005646; Lee MD, et al. J Immunother Cancer 2021;9:e002292.
[l] Renal biopsy may help distinguish between ICI versus non-ICI–related toxicities; however, initiation of steroids should not be delayed while waiting for biopsy.
[m] Data supporting use of these agents are limited.
[n] Lin JS, et al. Oncoimmunology 2021;10:1877415.

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

PRINCIPLES OF IMMUNOSUPPRESSION FOR PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITOR IMMUNOTHERAPY

General Principles

- Close consultation with disease-specific subspecialties is encouraged.
  - Referral to a tertiary care center may be required for management of complex cases or multi-system irAEs.
- Selected irAEs including hypothyroidism and other endocrine irAEs may be treated with hormonal supplementation, without the need for steroid therapy. See Endocrine Toxicities section.
- Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. Due to the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy.
- Combination therapies with non-ICI agents (eg, vascular endothelial growth factor [VEGF] inhibitors) may complicate irAE workup due to overlapping toxicity. If low suspicion of irAE, consider holding non-ICI therapy and monitoring before use of immunosuppression.
- An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Principles of Steroid Use in the Management of irAEs

- We recommend early intervention with steroids for the general management of immune-related toxicity.
- If unable to taper steroids, steroid-sparing measures with secondary agents may be appropriate to minimize steroid exposure and expedite resumption of ICI therapy.
- In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with steroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
- Steroid Dosing
  - See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see the Principles of Immunotherapy Rechallenge (IMMUNO-C) for guidance by organ site.
  - Higher potency (eg, Class 2 or 3) topical steroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
  - Prednisone is the preferred oral steroid due to ease of dosing and wide availability. IV methylprednisolone is the preferred IV steroid.
- Steroid Taper
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis, hepatitis, and neuromuscular toxicities.
  - Patients who are initiated on longer steroid tapers should have close follow-up with oncologist or co-managing disease-specific subspecialist team to monitor for side effects of steroid use, and to evaluate any need for modifying immunosuppressant regimen as appropriate based on clinical improvement of irAE.

Continued

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

PRINCIPLES OF IMMUNOSUPPRESSION FOR PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITOR IMMUNOTHERAPY

- **Prophylaxis**
  - **Infection**
    - ◊ ***Pneumocystis jirovecii*** **pneumonia (PJP) prophylaxis is recommended for patients expected to receive ≥20 mg daily prednisone equivalent for ≥4 weeks. Consider starting PJP prophylaxis if still steroid-dependent by the end of 2 weeks. Sulfamethoxazole-trimethoprim is preferred. For patients with a sulfa allergy, consider aerosolized/IV pentamidine. Consider avoiding atovaquone due to risk of diarrhea particularly in patients with colitis, and avoid dapsone due to risk of hemolytic anemia. Check glucose-6-phosphate dehydrogenase (G6PD) screen prior to dapsone use. See** **NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections****.**
    - ◊ **Other fungal infections are rare, and the utility of prophylaxis for these infections is unclear. Patients receiving extended immunosuppression may be at higher risk of an invasive fungal infection.**
    - ◊ **Prophylaxis against HSV or VZV reactivation can be considered. See** **NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections****.**
  - **Gastritis**
    - ◊ **PPI therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of steroid therapy. Consider prescribing full-dose PPI when the patient is taking high-dose steroids.**
  - **Osteoporosis**
    - ◊ **If patients need to be on steroids long-term, they are at risk for developing osteoporosis. Vitamin D and calcium supplementation should be provided to prevent osteoporosis. Refer patient to physical therapy and to endocrinology; weight-bearing exercises are recommended.**
    - ◊ **Steroid use of >30 mg for >30 days puts patients at high risk for vertebral fractures. Depending on clinical context, consider use of agents to maintain bone mineral density.**

Pathogen Reactivation

- **There is a risk for hepatitis B virus (HBV) reactivation with anti-TNFα agents, rituximab, or other immunosuppressive agents (eg, steroids). Test for HIV, hepatitis B (surface antigen and core antibodies), and hepatitis C prior to TNF inhibition and monitor HBV/HCV carriers during and for several months after therapy.**
- **There is a risk for TB activation. Test for latent/active TB prior to TNF inhibition. TB testing should not delay initiation of anti-TNFα agents for the management of irAEs.**
  - **Results of TB testing need not be finalized prior to dosing anti-TNFα agents in the acute setting.**
  - **Interferon-gamma release assays for TB testing are preferred.**
- **For individuals starting on steroids who were born or who have lived for >3 months in areas endemic for *Strongyloides* such as Central or South America, Southeast Asia, and Africa, would send *Strongyloides* IgG serology and either treat for positive serology, or treat empirically with ivermectin 0.2 mg/kg daily x 2 days and repeat in 2 weeks for total of 4 doses.**

Continued

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

PRINCIPLES OF IMMUNOSUPPRESSION FOR PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITOR IMMUNOTHERAPY

Principles of Immune Checkpoint Blockade in Patients with Pre-Existing Autoimmune/Viral Conditions or Organ Transplant Recipients

- **Patients with a history of HIV or viral hepatitis may be candidates for immunotherapy. See the NCCN Guidelines for Cancer in People with HIV.**
- **Patients with pre-existing autoimmune conditions or organ transplant recipients may be candidates for immune checkpoint blockade.**
- **Patients with autoimmune neurologic conditions or life-threatening autoimmune disorders, particularly if not controlled with immunosuppressive medications or requiring high doses of immunosuppression, are unlikely to be suitable candidates for cancer immunotherapy.**
- **Patients with prior allogeneic hematopoietic cell transplant (HCT) may be candidates for immunotherapy.**

Considerations for Patients with Pre-existing Autoimmune Conditions
- **Anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)-based therapy has a higher incidence of exacerbating baseline autoimmune conditions relative to anti-programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1)–based approaches.**
- **Optimization of immunosuppression for pre-existing autoimmune conditions, including close follow-up with pertinent subspecialists, is recommended.**
  - **Goal of immunosuppressive regimen allowing for dose of prednisone <10 mg daily or equivalent prior to initiating cancer immunotherapy.**

Considerations for Organ Transplant Recipients[1]
- **Graft failure while on cancer immunotherapy has been reported. Transplant organ loss may be an outcome of treatment with cancer immunotherapy and should be discussed with patient and organ transplant team. The risks and benefits of ICI therapy in patients with organ transplantation are very complex. Please refer to transplant team prior to starting immunotherapy in such patients.**
  - **Patients with solid organ transplantation who have a viable option for alternative therapy if there is graft rejection (eg, kidney) may be candidates for immunotherapy, particularly if there is no prior evidence of graft rejection and if the patient is on maintenance immunosuppression.**

Consideration for Patients with Prior Allogeneic HCT
- **There is an increased risk of transplant-related complications, including potentially fatal graft-versus-host disease (GVHD).**
- **Careful discussion with patient and allogeneic HCT physicians should precede initiation of immunotherapy.**

[1] Portuguese AJ, et al. J Natl Compr Canc Netw 2022;20:406-416.

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

PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

HEALTH CARE PROVIDER (HCP) INFORMATION

Prior to Starting Immune Checkpoint Inhibitor (ICI) Therapy[a]:
- Assess patient's understanding of disease and recommendations for treatment.
- Educate patients about mechanism of action and rationale for use of ICIs.
- Document any underlying medical conditions affecting any organ system (eg, pulmonary, cardiac, neurologic, musculoskeletal).
- It is important to take a history of any autoimmune diseases.
- Record all medications, including over-the-counter medications and herbal supplements.
- Patients of childbearing potential should be advised to use effective birth control during and for at least 5 months after the final dose of immunotherapy.
  - The effect of immunotherapy on human reproductive function is unknown. Consider fertility preservation and reproductive endocrinology referral for all patients starting therapy who have not yet completed family planning.
- Breastfeeding is contraindicated during and for at least 5 months after the final dose of immunotherapy.
- Provide patients with and instruct them to carry a wallet card that outlines the type of immunotherapy they are receiving, potential irAEs, and contact numbers for their oncology health care team.
- Assess patient's ability to monitor and report potential irAEs. Engagement of caregiver may be necessary.
- Assess patient for potential for home care support service needs during therapy.
- Educate patient about the potential toxicity profile of ICI therapy, including presenting symptoms and timing.
- Inform patient of existing educational resources:
  - NCCN Guidelines for Patients
  - Understanding Immunotherapy Side Effects
  - Oncology Nursing Society: Immunotherapy Wallet Cards

Instruct Patients to Notify the Oncology Health Care Team if:
- Any new signs or symptoms develop, including severe fatigue, headache, rash, cough, shortness of breath, chest pain, abdominal bloating, change in bowel pattern, weight loss, vision changes or eye pain, severe muscle weakness, severe muscle or joint pains, and/or mood changes.
  - irAEs can occur after completion of therapy. Patients should monitor symptoms for at least 2 years following the conclusion of immunotherapy.
- Patient is evaluated by other HCPs or admitted to the hospital.
- Any new medications are prescribed, or prior to receiving any immunizations or vaccinations.
  - Vaccines that are inactivated or killed, or mRNA (eg, COVID vaccines) preparations are permissible during a course of immunotherapy. Due to the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy.
- Patients are experiencing ICI-T1DM and/or ICI-hypophysitis with adrenal insufficiency. These patients are recommended to wear a medical alert bracelet, ensure adequate supply of medications if traveling, and notify their oncologist or endocrinologist in advance of scheduled procedures or in case of acute illness as medication doses may need to be adjusted. See ENDO-3 for recommendations on stress dose steroids.

[a] Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

Continued

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

PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

HEALTH CARE PROVIDER (HCP) INFORMATION

Toxicity Management[a]:

- **Review patient medications for potential drug interactions (eg, QT prolongation) when administering agents to manage ICI-related toxicity.**
- **Mild to moderate AEs:**
  - **Provide symptomatic management.**
  - **Delay in immunotherapy may be recommended if unclear if irAE is developing or until AEs resolve to grade 1 or pre-treatment baseline.**
  - **Steroids may be required if AE does not improve. If hormone replacement is required, it is usually for lifetime and may continue beyond the completion of therapy with ICIs.**
- **Severe AEs:**
  - **Discontinue immunotherapy.**
  - **Initiate steroid therapy immediately. IV methylprednisolone should be considered until there is evidence of improvement in toxicity.**
  - **Additional immunosuppressant therapy may be required for steroid-unresponsive AEs.**
  - **Inpatient care and additional supportive care may be required.**
  - **Ensure appropriately timed follow-up visits with oncologist or co-managing disease-specific subspecialist team for patients who required hospitalization for severe AEs. Close monitoring is encouraged as these patients are likely to have been started on new medications such as immunosuppressive agents and hormone replacement therapy that may require further adjustment or re-evaluation after hospitalization.**
- **Supportive care during immunosuppressant therapy may include the following:**
  - **Monitoring of blood glucose levels**
  - **PPIs or H2 blockers to prevent gastritis**
  - **Antimicrobial and antifungal prophylaxis to prevent opportunistic infections**
  - **Vitamin D and calcium supplementation to prevent osteoporosis**

[a] Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

Continued

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

PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

PATIENT EDUCATION CONCEPTS

- **Educational efforts must consider the patient's primary language and literacy level.**
- **Education should be provided at the start of therapy and at regular intervals as the trajectory of irAEs is variable. Reinforcement of educational concepts is essential.**

Immunotherapy Background:
- **One of the functions of the immune system is to distinguish healthy cells from abnormal cells. Tumor cells have proteins on their surface that bind to immune cells, blocking the ability of the immune cell to recognize them as foreign.**
- **ICIs are a class of medications that prevent tumors from "hiding" or "evading" the body's natural immune system. ICIs block the proteins referred to above, "releasing the brakes" on the immune system's white blood cells (WBCs).**
- **ICI therapy may be given in combination with other ICIs, chemotherapy, or targeted therapy.**

Side Effects (AEs):
- **AEs from immunotherapy differ from those of other types of cancer treatment and can affect one or several different organ systems.**
- **Amplifying the immune system can cause T cells to attack healthy cells in the body, causing inflammatory conditions that mimic a range of autoimmune conditions, some of which can be serious. These are known as irAEs.**
- **irAEs can occur at any time during treatment or after treatment is completed. irAE rebound during steroid taper can also occur, which may impact steroid taper.**
- **The severity of AEs can range from asymptomatic to severe or life-threatening. They may be cumulative over the course of therapy.**
- **Combination therapy may increase the severity of AEs. This can occur when immunotherapy is combined with chemotherapy, targeted agents, radiation therapy, or other types of immunotherapy.**
- **Some immune-related toxicities (eg, inflammatory arthritis, pneumonitis) may become chronic/require long-term management (Braaten TJ, et al. Ann Rheum Dis 2020;79:332-338; Johnson DB, et al. Cancer Immunol Res 2019;7:1755-1759; Naidoo J, et al. J Immunother Cancer 2020;8: e000840).**

Monitoring and Treatment Response[a]:
- **Therapy with ICIs requires close communications between patient/family and the treating center. Symptoms that patients may think are unrelated (eg, diarrhea or nausea) are often signs of ICI toxicity.**
- **Educate patients to notify all HCPs (especially primary care physicians [PCPs]) that they are receiving/have received immunotherapy.**
- **Regular monitoring will be conducted to detect any potential irAEs and to assess treatment response.**
- **Laboratory tests should be obtained prior to each treatment and at regular intervals after completion of immune checkpoint blockade to assess for organ function (eg, CMP; kidney, liver, thyroid, pancreas).**
- **Physical exams will include monitoring of organ function (eg, cardiac, pulmonary, neurologic, skin).**
- **Assess for significant shifts in weight, as they may be indicative of fluid balance disorders.**
- **Treatment response time differs from standard cancer therapy; it may take longer to see a response than with other types of cancer therapy.**
- **Most irAEs can be managed effectively if detected and treated early.**

[a] Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

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

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

General Principles

- **Discuss the risks/benefits of restarting immunotherapy with the patient.**
- **About 1 in 3 patients may have recurrence of the same irAE after rechallenge.[a] Exercise caution when considering resumption of immunotherapy after significant irAEs. With some exceptions, resumption of immunotherapy following grade 2–3 irAEs can be considered on resolution to ≤ grade 1. Monitor closely for recurrent symptoms.**
  - **If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.**
  - **If an objective response (complete or partial) to ICI therapy was achieved, resumption of immunotherapy may not be necessary. The risk of toxicity on resumption may outweigh benefit.**
- **IrAEs that respond to immunosuppressive therapies may pose a lower risk for rechallenge.**
- **Permanent discontinuation of a given class of immunotherapy may be warranted for severe irAEs or for some moderate irAEs with high risk of morbidity/mortality. For example, if a patient experiences grade 3 or 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with a PD-1 or PD-L1 monotherapy after resolution of the earlier toxicity.**
- **Consult with organ-specific specialists prior to resumption of immunotherapy as appropriate following an immunotherapy hold due to irAEs.**

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Cardio-vascular	• Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
Endocrine	• Thyroid: No discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Hypophysitis manifested by deficiency of ACTH, TSH, and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: Immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): Hold immunotherapy until resolution of symptoms after steroid therapy and hormone replacement is initiated; consider resumption of immunotherapy after symptoms related to mass effect are resolved. • T1DM with DKA: Consider resuming once DKA has been corrected and glucose level has stabilized. • Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue.
Eye	• Hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology.

[a] Dolladille C, et al. JAMA Oncol 2020;6:865-871.

Continued

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

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

GI	• After grade 2 colitis, may consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. For grade 3 colitis, if combination ICI therapy was used previously, consider resumption of monotherapy with anti-PD-1 or anti-PD-L1. The risk of recurrent colitis is dependent on agent and/or combination resumed (ie, CTLA-4 +/- PD-1>PD-1+ LAG-3>PD-1). In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. Consider concurrent vedolizumab on immunotherapy resumption. • Esophagitis/gastritis/duodenitis: Once symptom remission on medical management has been achieved, immunotherapy rechallenge can also be considered with the same strategy as colitis, although high-level evidence is still lacking. • Discontinue if irAE is serious or life-threatening. Do not make up doses missed due to irAE and/or required steroid treatment.
Hematologic	• Hemolytic anemia, HLH-like syndrome: Consider resumption of immunotherapy in consultation with hematology. • Aplastic anemia: For severe or very severe, discontinue. For non-severe, consider resumption of immunotherapy in consultation with hematology. • Thrombocytopenia: Rechallenge upon resolution of platelet count to ≤ grade 1 (or prior baseline), and treatment for thrombocytopenia has been discontinued.
Kidney	• Hold immunotherapy per guidelines; on resolution to ≤ stage 1, consider resuming concomitant with or without steroid if creatinine is stable. • After restarting immunotherapy, monitor creatinine every 2–3 weeks or more frequently as clinically indicated. If creatinine remains stable, consider longer durations between creatinine checks. Gupta S, et al. J Immunother Cancer 2022;10:e005646. • Consider permanent discontinuation in the setting of severe (grade 3–4) proteinuria (Discussion). • For resolved stage 2 and/or stage 3 renal irAE, consider permanent discontinuation if possible; may consider re-challenge if clinically indicated, at least after ≥2 months of holding ICI therapy. • If the patient has partial or complete recovery after AKI, consider rechallenge after discussion with nephrology.
Liver	• Transaminitis without synthetic liver dysfunction: Following a grade 2 irAE, may consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • Permanently discontinue immunotherapy in the setting of G4 synthetic liver dysfunction and/or permanent biliary strictures requiring endoscopic retrograde cholangiopancreatography (ERCP).
Lung	• Progressive grade 1 pneumonitis requiring a hold: Consider resuming on radiographic evidence of improvement. • Grade 2/3: Consider resuming once pneumonitis has resolved to ≤ grade 1 and patient is off steroids. • Permanent discontinuation is warranted in the setting of severe (grade 4) pneumonitis.
Musculo-skeletal	• Inflammatory arthritis, myositis, PMR, GCA (moderate to severe irAE requiring hold): Resume on stabilization, or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis, PMR, or GCA that significantly impairs ADLs and quality of life. • Severe or life-threatening myositis (with or without myocarditis): Consider permanent discontinuation in select patients due to high risk of morbidity/mortality.

Continued

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

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Nervous System	• Myasthenia gravis/myasthenia gravis-like syndrome: Permanently discontinue immunotherapy after grade 3–4 AE. • GBS: Discontinue immunotherapy for severe (grade 3–4) GBS. • Peripheral neuropathy: Following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: Consider resuming following mild to moderate AE if symptoms resolve to grade 0. • Encephalitis: Discontinuation is warranted in the setting of severe encephalitis. • Demyelinating disease: Discontinuation of immunotherapy following any-grade AE.
Oral Mucosa	• Consider rechallenge after symptoms become grade 1, or mild in the case of oral dysesthesia. • Discuss risks of potential worsening symptoms compared with benefits for patients with moderate to severe Sicca or dysesthesia symptoms.
Pancreas	• Symptomatic grade ≤3 pancreatitis: Consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in lipase. Consider consultation with relevant pancreatic specialist regarding resumption. • Permanent discontinuation is warranted for severe (grade 4) pancreatitis and other related complications (eg, abscess, fistula)
Skin	• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN. • Psoriasis and lichen planus: Rechallenge may be considered if symptoms are controlled and extent of BSA is <30%, especially if the patient is on targeted biologic.

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

ABBREVIATIONS

AChR	acetylcholine receptor
ACTH	adrenocorticotropic hormone
ADEM	acute demyelinating encephalomyelitis
ADL	activities of daily living
AE	adverse event
AFB	acid-fast bacilli
AKI	acute kidney injury
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	antineutrophil cytoplasmic antibody
AST	aspartate aminotransferase
ATG	antithymocyte globulin
BAL	bronchoalveolar lavage
BNP	b-type natriuretic peptide
BRAT	bananas, rice, apple sauce, toast
BSA	body surface area
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CBC	complete blood count
CCP	cyclic citrullinated peptide
CGM	continuous glucose monitoring
CK	creatine kinase
CMP	comprehensive metabolic panel
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CRS	cytokine release syndrome
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSF	cerebrospinal fluid
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
DAT	direct antiglobulin test
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DRESS	drug reaction with eosinophilia and systemic symptoms
dsDNA	double-stranded DNA
ECG	electrocardiogram
EEG	electroencephalogram
EGD	esophagogastroduodenoscopy
EMG	electromyogram
ENT	ear, nose, and throat
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
FSH	follicle-stimulating hormone
FT4	free thyroxine
G6PD	glucose-6-phosphate dehydrogenase
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome
GCA	giant cell arteritis
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GI	gastrointestinal

Continued

ABBREVIATIONS

GVHD	graft-versus-host disease
H&P	history and physical
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care provider
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
Hb	hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	hemophagocytic lymphohistiocytosis
HSV	herpes simplex virus
HUS	hemolytic uremic syndrome
iADL	instrumental activities of daily living
ICI	immune checkpoint inhibitor
ICI-T1DM	immune checkpoint inhibitor-associated type 1 diabetes mellitus
ICU	intensive care unit
ID	infectious disease
IEC	immune effector cell
IEC-HS	immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
ILD	interstitial lung disease
INR	international normalized ratio
IO	immuno-oncology
IOP	intraocular pressure
irAE	immune-related adverse event
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LLN	lower limit of normal
LV	left ventricular
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MGFA	Myasthenia Gravis Foundation of America
MOG	myelin oligodendrocyte glycoprotein
MRCP	magnetic resonance cholangiopancreatography
NAAT	nucleic acid amplification test
NCS	nerve conduction study
NIF	negative inspiratory force
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
OCT	optical coherence tomography
PCP	primary care physician
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1

Continued

ABBREVIATIONS

PD-L1	programmed death ligand 1
PE	pulmonary embolism
PFT	pulmonary function test
PJP	*Pneumocystis jirovecii* pneumonia
PMR	polymyalgia rheumatica
PNH	paroxysmal nocturnal hemoglobinuria
PPI	proton pump inhibitor
PT/INR	prothrombin time/international normalized ratio
PTT	partial thromboplastin time
PUD	peptic ulcer disease
RBC	red blood cell
RF	rheumatoid factor
RNFL	retinal nerve fiber layer
RPR	rapid plasma reagin
RR	respiratory rate
RRT	renal replacement therapy
RSV	respiratory syncytial virus
sCR	serum creatinine
SJS	Stevens-Johnson syndrome
SPEP	serum protein electrophoresis
TB	tuberculosis
TEN	toxic epidermal necrolysis
TFT	thyroid function test
Tg	thyroglobulin
TNF	tumor necrosis factor
TPN	total parenteral nutrition
TPO	thyroid peroxidase
TRAb	TSH receptor antibody
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TTE	transthoracic echocardiogram
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
UPEP	urine protein electrophoresis
UTI	urinary tract infection
UVB	ultraviolet B
VC	vital capacity
VEGF	vascular endothelial growth factor
VZV	varicella zoster virus
WBC	white blood cell

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

All recommendations are category 2A unless otherwise indicated.

Discussion

This discussion corresponds to the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities. MS-2, MS-3, and MS-17 to MS-21 were updated on October 25, 2024. All other sections were last updated on April 8, 2019.

Table of Contents

Overview

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

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

Clinicians should be aware that toxicities related to cancer immunotherapy are autoimmune in nature and can impact essentially any organ system.[10] The toxicity profiles of cancer immunotherapy and management strategies for irAEs are distinct from those of traditional chemotherapy.[10,11] Early recognition and prompt intervention are key goals for the management of toxicities related to cancer immunotherapy.

In general, a multidisciplinary approach is recommended, and consultation with an appropriate specialist for evaluation and treatment is encouraged to ensure optimal patient outcomes. Unfortunately, obtaining a specialist consultation within an urgent timeframe can be challenging. Therefore, the guidelines provide initial steps for oncology clinicians to assess and manage a patient's irAE while minimizing disruption to cancer treatment, particularly in situations when access to a specialist is limited. The guidelines also provide guidance on when inpatient care is needed.

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

Guidelines Update Methodology

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

Literature Search Criteria

Prior to the update of the NCCN Guidelines for the Management of Immune Checkpoint-Inhibitor-Related Toxicities, an electronic search of the PubMed database was performed to obtain key literature in the management of immune checkpoint inhibitor-related toxicities published since the previous Guidelines update, using the search terms: checkpoint inhibitor or immune checkpoint, in combination with the terms toxicity, adverse, or safety. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[12]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV;

Guideline; Practice Guideline, Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[13] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

The Role of the Immune System in Cancer

Dynamic interactions take place between the immune system and cancer cells, whereby immune cells can detect genetic and cellular abnormalities present on cancer cells. Various mechanisms are in place to closely regulate the activation and function of immune system effectors. However, malignant cells can also modulate immune cell activity, thus evading recognition and destruction by the immune system. This section provides a brief overview of the relationship between the immune system and tumors, and how immunotherapy targets effector cells in the immune system to activate and enhance the antitumor response.

Immunosurveillance refers to the process by which the immune system can screen for, recognize, and respond to foreign pathogens or abnormal (ie, precancerous, cancerous) cells within the body. The theory of cancer immunosurveillance has been incorporated into the larger concept of cancer immunoediting, which details several phases of the interaction between cancer and the immune system: elimination, equilibrium, and escape. In the elimination phase, a strong response to an immunogenic tumor leads to successful elimination of tumor cells. When the immune system is unable to completely eliminate the tumor, a phase of equilibrium occurs whereby the tumor remains present without progression or metastasis. Persistent equilibrium can lead to the selection of cells that have mutated to resist or avoid the antitumor immune response. This is described as the escape phase, when tumor cells "escape" the antitumor immune response, leading to tumor growth and progression to cancer.[14-18]

Conditions or events that compromise the immune system can lead to cancer cells escaping immunosurveillance.[15,19,20] Once cancer cells have escaped immunosurveillance and have begun to proliferate, their genetic and phenotypic plasticity enable them to develop additional mechanisms by which the tumor can evade, thwart, or even exploit the immune system.[15,19,20]

The immune system is capable of mobilizing immune effector cells in response to cancer cells. Immunotherapies harness the immune system to attack and destroy tumors by regulating molecules involved in immune cell

activation. In doing so, immunotherapy seeks to activate or reactivate the antitumor immune response to overcome or circumvent the immune evasion or "escape" mechanisms employed by cancer cells and tumors.

Evolution of Cancer Immunotherapy

Initial approaches to immunotherapy for cancer are focused on enhancing the immune system's antitumor response by targeting cytokines and other molecules responsible for regulating immune cell activity. Some examples of earlier-generation cancer immunotherapy include interleukin-2 (IL-2) and interferon (IFN) alfa-2b, which have been used to treat malignancies such as melanoma and renal cell carcinoma (RCC). However, a low therapeutic index and suboptimal efficacy limit the use and impact of these agents.[21,22] Lenalidomide and pomalidomide, immunomodulatory agents used for treating multiple myeloma, represent another prior approach to cancer immunotherapy.[23,24] These agents have a complex mechanism of action that results in the costimulation of T cells and NK (natural killer) cells, increased IL-2 and IFN gamma production, and decreased IL-6 and tumor necrosis factor (TNF)-alpha levels, among other effects.[23-25] However, the landscape of cancer care has undergone a dramatic shift with the recent approval of a new generation of cancer immunotherapies during the past 8 years.

Notable new treatments that have recently received FDA approval include ICIs and CAR T-cell therapies. ICIs comprise a novel class of agents that target immune cell "checkpoints," such as programmed cell death-1 (PD-1; eg, nivolumab, pembrolizumab[26,27]) and PD-1 ligand (PD-L1; eg, atezolizumab, avelumab, durvalumab[28-30]), as well as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4; eg, ipilimumab,[31] tremelimumab [under investigation]). Indications for ICIs have expanded dramatically and now include patients with lung (non-small cell and small cell cancers), head and neck, bladder, kidney, gastric, ovarian, and liver cancers, as well as melanoma, Hodgkin lymphoma, Merkel cell carcinoma, and tumors deficient in DNA mismatch repair mechanisms. ICIs, which were initially indicated for pretreated advanced disease, have moved into earlier treatment settings.[26]

Immune Checkpoint Inhibitors

Some of the most effective immunotherapies to date target immune checkpoints exploited by cancers to decrease immune activity. This section will provide a general overview of the mechanism of action of ICIs and discuss what is known regarding ICI-mediated immune dysfunction. For a discussion of the efficacy data for ICIs, please see the NCCN Guidelines for Treatment of Cancer by Site at www.NCCN.org.

Mechanism of Action

T-cell activation is an essential component of antitumor immunity, requiring costimulation through more than one mechanism. Binding of antigen-specific T-cell receptor (TCR) to major histocompatibility complex (MHC) on antigen-presenting cells (APCs) must be accompanied by costimulatory signals. CD28 is a well-characterized costimulatory factor expressed on T cells. Adequate CD28 binding to B7 family of costimulatory factors (CD80 [B7-1] or CD86 [B7-2]) on APCs is required for T-cell proliferation and full activation. The presence of growth factors such as IL-2 promotes T-cell differentiation and survival.[32,33]

Since unopposed immune activation can lead to a number of tissue-damaging consequences, the immune system has evolved to have complex self-regulatory mechanisms to control or dampen immune responses. This immunologic tolerance is maintained through a variety of mechanisms that include regulatory immune cells, immunosuppressive cytokines and chemokines, and immune checkpoint signaling. Immune checkpoint proteins such as CTLA-4 and PD-1 are closely regulated by immune cells to modulate T-cell activity. When bound by endogenous ligands, these receptors initiate a signaling cascade that suppresses T-cell

activation, limiting the immune response. Cancer cells coopt the various mechanisms of immune tolerance, including immune checkpoints to evade recognition by the immune system. Antibodies have been designed to bind these receptors to prevent receptor-ligand interaction, thus removing inhibition of T-cell activation. In doing so, the inhibitory interactions between tumor cells and infiltrating T cells are blocked, reversing T-cell tolerance. This process "releases the brake" on the immune response, promoting the immune system to mount an antitumor response.[34-43]

CTLA-4 Inhibitors

CTLA-4 is expressed by CD4+ (helper), CD8+ (cytotoxic) T cells, as well as regulatory T cells (Tregs). CTLA-4 functions as an early inhibitory signal during the priming phase for T-cell activation, typically within the lymph nodes. CTLA-4 cell surface expression is upregulated by several factors including TCR activation and certain cytokines. Early studies identified CTLA-4 as a negative regulator of T-cell activation through its high-affinity binding to costimulatory factors of the B7 family (ie, CD80 and CD86) at the surface of APCs. CTLA-4 outcompetes CD28 for binding to costimulatory factors on APCs, acting as a brake on this mechanism for T-cell activation by reducing IL-2 production and T-cell proliferation and survival. The relative degree of signaling through CD28/B7 versus CD28/CTLA-4 determines activation versus anergy of T cells.[32,33,44-47] Subsequent studies revealed the potential role of CTLA-4 blockade in the antitumor response.[48] CTLA-4 blockade results in greater numbers of effector T-cell clones becoming active and proliferating while reducing the immunosuppressive activity of Tregs.[33,49,50]

PD-1/PD-L1 Inhibitors

PD-1 receptor is present on the cell surface of various immune cells such as T cells, B cells, and NK cells. Its ligands, PD-L1 and PD-L2, have differential tissue expression. PD-L1 is expressed by a wide variety of tissues types, including tumor cells, whereas PD-L2 expression is mainly restricted to hematopoietic cells. PD-1 signaling exerts an inhibitory effect during the effector phase through inhibition of previously activated T cells primarily in the peripheral tissues. It decreases T-cell proliferation through reduced production of IFN-gamma, TNF alpha, and IL-2. In addition to blocking tumor cell apoptosis, PD-1 interaction with PD-L1/2 can lead to the progressive loss of T-cell functions (ie, T-cell exhaustion) and drive the conversion of T effector cells to Treg cells with immunosuppressive properties.[33,51-56] Studies have implicated PD-1 signaling in the antitumor response.[57] Blockade of the PD-1/PD-L1 interaction can lead to the reactivation of T-cell populations that have become exhausted following prolonged antigen exposure, such as quiescent antitumor T cells.[33,52,58]

ICI-mediated Immune Dysfunction

The pharmacodynamics and pharmacokinetics of ICI immunotherapy differ greatly from that of cytotoxic chemotherapy or targeted anti-cancer therapy.[59] Similarly, anti-CTLA-4 and anti-PD-1/PD-L1 immunotherapies are associated with toxicity profiles that are distinct from those observed with conventional anti-cancer therapies, though their presentation may at times be similar.[60-66] Whereas traditional cytotoxic chemotherapy often results in acute-onset emetic and myelosuppressive effects, irAEs tend to be relatively delayed-onset and inflammatory or autoimmune in nature.[67-70]

Although the pathophysiology of ICI-related irAEs is not yet fully elucidated, knowledge regarding the role of immune checkpoint pathways in autoimmune disease provides some clues. Many autoimmune diseases are related to failure of T-cell tolerance and uncontrolled activation of immune effector cells. Alterations in the genes encoding immune checkpoint proteins have been implicated in autoimmune disease. CTLA-4 and PD-1 polymorphisms have been linked to human autoimmune diseases including Celiac disease, diabetes mellitus, lupus, rheumatoid arthritis, and autoimmune thyroid disease. The spectra of irAEs associated with blockade of immune checkpoints falls in line with the phenotypes

observed as a result of mutations in the genes encoding CTLA-4 and PD-1 and has considerable overlap across the various ICIs.[71-74]

The precise pathophysiology of ICI-mediated irAEs is currently unknown. Translational research provides some evidence that irAEs may result from some combination of autoreactive T cells, autoantibodies, and/or proinflammatory cytokines (eg, interleukin-17).[73,75] One potential mechanism is T-cell activity directed at antigens present in both tumor cells and healthy tissue.[76,77] Inflammation in otherwise normal tissues could result from elevated levels of inflammatory cytokines as a downstream effect of T-cell activation.[78-81] Additionally, direct binding of immune checkpoint antibodies to targets expressed in normal tissues (eg, CTLA expression in the pituitary) could lead to complement-mediated inflammation.[82,83] Finally, immunotherapy might increase the levels of preexisting autoreactive antibodies.[84]

Early- and later-onset irAEs may result from distinct mechanisms that have yet to be elucidated. Typical earlier-onset, common irAEs appear to involve generalized epithelial inflammation and may be observed in the form of rash, colitis, and pneumonitis. These irAEs typically involve recruitment of neutrophils into normal tissues. Later-onset irAEs, which are typically less common, can include neurologic events and hypophysitis, among others. These tend to be more localized, organ-specific reactions. Research is ongoing into the specific mechanisms underlying irAEs associated with specific ICIs.

Incidence and Prevalence of irAEs

The incidence and prevalence of ICI-related toxicity is still being fully elucidated; much of the existing figures are based on trials of ipilimumab, pembrolizumab, and nivolumab. Comprehensive irAE data on newer agents are still being collected and analyzed. Due to the nature of irAEs and inconsistent reporting, it is likely that reported rates underestimate the actual incidence of these events. The reported incidence of any-grade irAEs associated with single-agent ICI treatment ranges widely across agents and trials, from approximately 15% to 90%.[85,86] Severe irAEs requiring immunosuppression and hold or discontinuation of treatment are estimated between 0.5% and 13% for monotherapy.[85] Analysis of pooled trial data found that 43% of patients discontinued combination therapy (nivolumab/ipilimumab) due to AEs, with gastrointestinal (GI) events being the most commonly reported reason for discontinuation.[87] ICI immunotherapies have been associated with rare AEs that are still in the process of being identified and studied at high-volume centers.

Single-Agent Therapy

CTLA-4

A 2015 meta-analysis by Bertrand et al examined data from 1265 patients across 22 clinical trials of anti–CTLA-4 antibodies (ipilimumab [n = 1132] and tremelimumab [n = 133]), reporting an overall incidence of 72% for any-grade irAEs and 24% for high-grade irAEs.[88] The most commonly observed AEs were dermatologic and GI, followed by endocrine and hepatic events. A randomized, double-blind, phase III trial in patients with unresectable or metastatic melanoma revealed a dose-dependent effect in treatment-related AEs for patients receiving ipilimumab at a dose of 3 mg/kg (n = 362) or 10 mg/kg (n = 364).[89] High-grade irAEs were reported in 18% and 30% of the 3 mg/kg and 10 mg/kg treatment groups, with 2 and 4 treatment-related deaths, respectively. The most common high-grade AEs, including diarrhea, colitis, elevated liver enzymes, and hypophysitis, were all more common at the higher dose of ipilimumab.[89] Adjuvant use of ipilimumab (10 mg/kg) for resected stage III melanoma appears to be associated with a higher incidence of AEs. Based on phase III data in patients receiving adjuvant ipilimumab (n = 475), the incidence of high-grade irAEs was 41.6% with 5 fatalities (1.1%).[90,91]

PD-1/PD-L1

For PD-1/PD-L1 inhibitors, the reported overall incidence of any-grade irAEs was up to 30% based on patients in phase III trials.[86,92-94] To date, the incidence of high-grade AEs associated with PD-1/PD-L1 inhibitors appears to be somewhat less dose-dependent than ipilimumab and to vary by disease site.[85] In a recent meta-analysis of anti-PD-1/PD-L1 agents, any-grade and severe-grade irAEs occurred in about 26.8% and 6.1% of patients, respectively.[95] Rates of high-grade irAEs were similar across pembrolizumab, nivolumab, and atezolizumab, ranging from 5% to 8%.[95]

De Velasco and colleagues recently reported on the incidence of the most common ICI-associated irAEs in a meta-analysis of 21 randomized phase II/III trials conducted from 1996 to 2016, which included a total of 6528 patients who received monotherapy (atezolizumab, n = 751; ipilimumab, n = 721; nivolumab, n = 1534; pembrolizumab, n = 1522) and 4926 patients in placebo or standard therapy control arms using chemotherapy or biologic agents.[96] Due to inconsistent recognition and reporting of less-common irAEs in the clinical trial data, this meta-analysis was limited to examination of 5 common and well-documented types of irAEs: colitis, liver toxicity (AST elevation), rash, hypothyroidism, and pneumonitis. When compared to patients in trial control arms, patients receiving ICIs were found to be at greater risk for any-grade immune-related colitis, AST elevation, rash, hypothyroidism, and pneumonitis. Within this cohort, across all ICIs, the incidence of grade 3/4 events was 1.5% for colitis, 1.5% for liver toxicity, 1.1% for rash, 0.3% for hypothyroidism, and 1.1% for pneumonitis. High-grade colitis and rash were significantly more common among patients on ipilimumab than in those receiving PD-1/PD-L1 inhibitor.[96] In a separate review of the data, Kumar and colleagues also compared the risk of developing certain irAEs with different classes of ICIs.[85] While ipilimumab was associated with higher rates of colitis, pruritus, rash, and hypophysitis, PD-1/PD-L1 inhibitors resulted in a higher risk for developing vitiligo (typically observed in patients with melanoma), thyroid dysfunction, hepatotoxicity, and pneumonitis.[85]

De Velasco et al compared the risk of developing specific irAEs by tumor type (melanoma, lung, and other), reporting no significant differences for all-grade or high-grade irAEs.[96] Khoja et al also conducted a systematic review of irAEs by ICI class and tumor type in 6869 patients from 48 trials between 2003 and 2015,[97] with probable considerable overlap in patient population from the De Velasco study. Although most findings were similar, Khoja and colleagues' findings deviated slightly when analyzing irAE incidence according to tumor histology in patients treated with PD-1 inhibitors. They found that patients with melanoma experienced higher incidence of GI and skin irAEs but a lower incidence of pneumonitis compared with NSCLC. Patients with melanoma experienced arthritis and myalgia more commonly than those with RCC, but patients with RCC experienced higher frequency of pneumonitis and dyspnea. However, comparisons of irAE incidence across disease type were not adjusted for patient factors such as smoking history and age. Similar comparisons were not possible for CTLA-4 blockade since the majority of available data was on patients with melanoma.[97]

The safety data for PD-L1 inhibitors are still maturing and data collection is ongoing. Comparison of irAE incidence for PD-1 versus PD-L1 inhibitors have been calculated primarily from data published on patients with non-small cell lung cancer (NSCLC). A 2018 meta-analysis compared the data on toxicity profiles of PD-1 and PD-L1 inhibitors from 23 studies that occurred between 2013 and 2016 (PD-1: n = 3284; PD-L1: n = 2460).[98] A near-significant trend revealed irAEs to be more common with PD-1 versus PD-L1 blockade (16% vs. 11%; *P* = .07). However, the incidence of severe irAEs was not significantly different between PD-L1 and PD-1 inhibitors, (5% vs. 3%, *P* = 0.4). Pneumonitis occurred twice as often with PD-1 inhibitors (4% vs. 2%; *P* = .01) and hypothyroidism was also more

common with PD-1 inhibitors (6.7% vs. 4.2%; P = .07).[98] Similar findings were reported in a 2017 meta-analysis of data on pneumonitis incidence with PD-1 inhibitors (12 trials, n = 3232) and PD-L1 inhibitors (7 trials, n = 1806).[99] For PD-1 versus PD-L1 inhibitors, the incidence for any-grade pneumonitis was 3.6% versus 1.3% (P = .001) and 1.1% versus 0.4% for high-grade pneumonitis (P = .02).[99]

Combination Therapy

Numerous ongoing studies are examining regimens that include ICIs given in combination with another ICI, chemotherapy, or targeted agent. While combination regimens offer the potential for enhanced efficacy, in general, observed toxicity with ICI-based combination regimens is greater than that for ICI monotherapy. Combined PD-1 plus CTLA-4 blockade triggers substantially more irAEs than anti-PD-1 agents alone, with high-grade events reported for 55% to 60% of individuals receiving combination therapy versus 10% to 20% of individuals receiving anti-PD-1 monotherapy.[100-102] Studies have begun to investigate the extent to which combination therapies pose clinical safety and tolerability challenges, and whether these challenges will limit their usefulness as anticancer therapy.[103-106]

The only current FDA-approved regimen using combined ICI therapy is nivolumab plus ipilimumab for treating advanced melanoma, RCC, or microsatellite-unstable tumors.[27,31] Nivolumab plus ipilimumab resulted in enhanced survival outcomes compared with ipilimumab monotherapy in advanced melanoma.[102,107] In the phase III CheckMate 067 trial of nivolumab plus ipilimumab versus ipilimumab or nivolumab monotherapy (n = 945, randomized in a 1:1:1 ratio), treatment-related AEs occurred in 96% of patients receiving combination therapy and 86% of those treated with monotherapy. Although no unique toxicities were identified in patients receiving ICI combination therapy, the incidence of high-grade irAEs for combination therapy (59%) was more than twice the incidence for single-agent nivolumab (21%) and ipilimumab (28%). The percentages of patients discontinuing treatment due to any-grade treatment-related AEs were 39%, 12%, and 16% for patients receiving combination therapy, nivolumab, and ipilimumab, respectively. Preliminary findings suggest that early discontinuation due to irAEs (after a median of 3 doses) may not compromise the survival benefit, as evidenced by a 3-year survival rate of 67%.[102]

The KEYNOTE-029 trial began to investigate whether standard-dose pembrolizumab in combination with reduced-dose ipilimumab may be more tolerable than full-dose ICI combinations.[108] Dose-modified nivolumab plus ipilimumab regimens are also under investigation for NSCLC and small cell lung cancer (SCLC),[109,110] and nivolumab plus ipilimumab is recommended by the NCCN Guidelines for Small Cell Lung Cancer.

Safety data have also been published for early-phase investigations of ICI therapy in combination with additional targeted agents or chemotherapeutics.[111-113] Immune checkpoint blockade given in combination with radiation therapy is also the subject of investigation.[114,115]

ICI Therapy-Related Fatal irAEs

A recently published systematic review and meta-analysis examined fatal irAEs from ICI therapy using data from multiple sources.[101] Meta-analysis of data from 112 published trials (n = 19,217) compared the rate of fatal irAEs by agent. Similar rates of fatal irAEs were reported for anti-PD-1 (0.36%) and anti-PD-L1 agents (0.38%), with significantly higher rates of fatal irAEs reported for anti-CTLA-4 monotherapy (1.08%) and anti-PD-1/PD-L1 + anti-CTLA-4 combination regimens (1.23%). For ipilimumab monotherapy, significantly fewer fatal irAEs occurred at the 3 mg/kg dose than 10 mg/kg dose. However, when used in combination with

anti-PD-1 therapy, no significant difference in fatal irAE rate was observed for ipilimumab at 1mg/kg versus 3 mg/kg dose.[101]

Examination of 613 cases of fatal ICI-related irAEs reported in the WHO pharmacovigilance database revealed that certain ICI agents were associated with a different spectrum of fatal irAEs.[101] The majority of fatal irAEs associated with ipilimumab monotherapy were due to colitis (70%), with smaller proportions of hepatitis and pneumonitis-related deaths. However, fatal irAEs with anti-PD-1/PD-L1 therapy were distributed more broadly: pneumonitis (35%), hepatitis (22%), colitis (17%), neurologic events (15%), and myocarditis (8%). Among the fatal irAEs reported for combination regimens (ipilimumab plus anti-PD-1/PD-L1), colitis was most common (37%), followed by myocarditis (25%), hepatitis (22%), pneumonitis (14%), and myositis (13%). When fatality rates were assessed across different types of irAEs, myocarditis was associated with the highest risk of death (52/131 cases, 39.7%). Fatality rates for patients with hepatitis, pneumonitis, nephritis, and neurologic events ranged between 10% and 17%, while ≤5% of hypophysitis, adrenal insufficiency, and colitis cases proved fatal.[101]

Finally, temporal patterns of fatal irAEs were examined using combined pharmacovigilance case reports and multicenter retrospective data review.[101] For irAEs that eventually proved fatal, symptom presentation occurred a median of 40 days after onset of monotherapy with ipilimumab or an anti-PD-1/PD-L1 agent, and 14.5 days after initiation of combination regimens. Median time to death after initiation of ipilimumab monotherapy, anti-PD-1/PD-L1 monotherapy, or combination regimen was 64, 43, and 35 days, respectively.[101]

IrAEs as a Biomarker of Treatment Response

Investigators have begun to examine whether developing certain ICI-mediated irAEs may be linked to improved treatment response and survival outcomes. An overview of the preliminary findings related to irAEs and treatment outcomes is provided below. Further research into this phenomenon is needed to explore potential patterns.

Historically, induction of cutaneous irAEs was suggested as a positive prognostic factor in patients with melanoma who received various types of immunotherapy.[116] A retrospective review found that cutaneous irAEs, particularly vitiligo, may be associated with improved treatment response with pembrolizumab.[117-119] In patients with melanoma who received nivolumab, rash and vitiligo were both associated with improved overall survival (OS).[120] The potential relationship between development of GI irAEs and survival outcomes has also been investigated. A retrospective analysis of 327 patients found an association between GI irAEs and OS, with diarrhea being an independent predictor of OS regardless of whether immunosuppressive therapy was required to manage this irAE.[121]

In a prospective cohort of 524 patients receiving ICI therapy, patients who developed rheumatologic irAEs had a higher tumor response rate compared with patients who experienced no irAEs (85.7% vs. 35.3%; $P < .0001$).[122] Additionally, early data suggest a possible association between the development of neurologic irAEs and favorable disease response. Durable disease response has been reported in the setting of neurologic irAEs despite early discontinuation of ICI.[123]

However, in a retrospective review of 298 patients who received ipilimumab for metastatic melanoma, the occurrence of any-grade irAEs was not associated with OS or time to treatment failure (TTF).[124] The authors also found no association between systemic corticosteroid therapy to manage irAEs and OS or TTF. Along similar lines, investigators have also questioned the impact of early discontinuation of ICI due to toxicity on antitumor efficacy and safety. Schadendorf et al examined pooled data from randomized phase II/III trials in which patients received combination nivolumab plus ipilimumab therapy (n = 409).[87] Therapy was discontinued

due to AEs in 176 patients, including 96 patients who discontinued therapy during the induction phase (in which the majority of high-grade AEs occurred). Overall response rate (ORR) was 58.3% for patients who discontinued therapy due to AEs during induction, versus 50.2% for those who did not discontinue therapy. Although similar, median OS was not reached for either group.[87]

Management of ICI-Related Toxicity

The primary facets of irAE management include recognition and grading of toxicity, immunosuppression, and individualized modification to ICI administration. Early recognition of symptoms and prompt intervention are key goals for the management of immunotherapy-related toxicity. Significant irAEs often necessitate holding immunotherapy, with permanent discontinuation of the class of agent associated with the toxicity in the setting of certain severe irAEs.

General Principles of Immunosuppression

Corticosteroids are the mainstay of treatment for most high-grade irAEs. Importantly, short-term use of corticosteroids to treat irAEs has not been shown to reduce anti-tumor efficacy. Appropriate duration and careful taper of corticosteroid therapy is important to prevent the recurrence of irAEs. Severe or steroid-refractory irAEs may require administration of additional immunosuppressive agents. For patients with severe irAEs not responsive to steroids within 48 to 72 hours, initiation of an additional immunosuppressant agent may be warranted in consultation with the relevant medical specialist. Close monitoring and follow-up should be performed to assess for response to corticosteroids and other immunosuppressants in the setting of ICI-related toxicity.

Tailored recommendations regarding the use of non-steroid immunosuppressants can be found in the individual irAE treatment algorithms and corresponding discussion sections. Selected endocrine irAEs may be treated with hormonal supplementation without the need for immunosuppression.

Immunomodulators

In these guidelines, recommendation for use of specific immune-modulating agents to manage irAEs are typically extrapolated from evidence for treating autoimmune conditions of the relevant organ system(s). Several commonly used immunosuppressants for managing steroid-refractory or severe irAEs are discussed below.

TNF inhibitors are a class of drugs widely used to block the inflammatory effects of TNF in autoimmune diseases.[125] Infliximab is a monoclonal anti-TNF-α antibody used for treating various autoimmune diseases, including Crohn's disease, ulcerative colitis, rheumatoid and psoriatic arthritis, and psoriasis.[125-127] Infliximab blocks the interaction of TNFα with its receptors, inhibiting induction of pro-inflammatory cytokines (IL-1, IL-6) and modulating the activity of immune effectors such as leukocytes, neutrophils, and eosinophils.[127,128] Infliximab has become a commonly used agent for treating steroid-refractory irAEs that develop during ICI therapy.[73,129] For patients with severe irAEs not responsive to steroids within 48 to 72 hours, early initiation of anti-TNFα therapy (ie, at 72 hours) may be warranted in consultation with the relevant medical specialist. Duration of therapy with TNF-alpha blockers for irAEs is not clearly defined, but is typically a single dose. A second dose of anti-TNFα therapy may be required, and can be administered 2 weeks after initial dose of infliximab. Anti-TNFα agents (eg, infliximab) are particularly effective in management of immune-related colitis and inflammatory arthritis (IA).

Vedolizumab is an integrin antagonist that binds to α4β7 integrin, blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), inhibiting the migration of T cells across the endothelium into inflamed GI tissues. Vedolizumab is currently indicated for treating GI inflammation due to ulcerative colitis and Crohn's disease.[130,131] Case

reports have described the use of vedolizumab for treating ICI-induced enterocolitis.[131,132] Vedolizumab may provide more specific immune suppression for the inflamed GI mucosa, hence theoretically sparing systemic immune suppression and anti-tumor immune responses.

Mycophenolate-containing medicines are immunosuppressive agents used for preventing organ rejection after transplant (ie, kidney, heart, liver). It is available as mycophenolic acid (MPA) or as mycophenolate mofetil (MMF), a prodrug of MPA.[133,134] These agents have multiple immunosuppressive actions, which result in decreased B- and T-cell proliferation, T-cell apoptosis, and suppression of dendritic cells and IL-1.[135,136] Published studies also support the clinical efficacy of these mycophenolate in various inflammatory or autoimmune conditions, such as autoimmune hepatitis, myositis, bullous disease, interstitial lung disease, and lupus nephritis, among others.[137-142] Retrospective analyses and case reports describe the use of mycophenolate in the management of steroid-refractory irAEs, including those involving the liver, kidney, pancreas, and eyes.[100,143-146]

Intravenous immunoglobulin (IVIG) has been used to suppress a wide array of autoimmune and chronic inflammatory conditions.[147,148] It is comprised of pooled IgG immunoglobulins harvested from the plasma of healthy blood donors and prepared for intravenous (IV) administration. The immunomodulatory mechanisms of IVIG are not fully understood, but it is known to modulate the activity and effector functions of B and T lymphocytes, impacting antigen presentation, pathogenic autoantibodies, complement system, and cytokines.[148-150] Efficacy has been demonstrated in neurologic inflammatory or autoimmune conditions such as Guillain-Barré syndrome (GBS), myasthenia gravis, neuropathies, rheumatologic conditions, blistering disorders, immune hematologic conditions, and many others.[151,152]

Plasmapheresis is a type of therapy that may be indicated when a substance in the plasma, such as immunoglobulin, becomes acutely toxic, as can occur during certain autoimmune reactions. During plasmapheresis, the blood contents are separated extracorporeally, resulting in removal of the plasma and subsequent therapeutic plasma exchange via infusion. Indications for which this procedure is a first-line therapy include neurologic conditions such as myasthenia gravis and GBS, but it is also indicated for various other autoimmune conditions.[153] Plasmapheresis (and IVIG) is often indicated as a second-line therapy for managing neurologic irAEs after limited or non-response to initial high-dose corticosteroid.[154] However, success in treating severe and often rapidly progressive neurologic irAEs has been mixed.[154-156]

Additional agents that have been used less frequently as part of advanced lines of immunosuppressive therapy include rituximab, tacrolimus, tocilizumab, cyclosporine, cyclophosphamide, methotrexate, and antirheumatic agents (eg, sulfasalazine, leflunomide).

Considerations for Patients on Immunosuppressants

Additional supportive care measures are needed for patients receiving an immunosuppressive regimen. Hyperglycemia, gastritis, opportunistic bacterial or fungal infections, and osteoporosis can occur with a longer-term systemic corticosteroid.[157-162] The panel recommends blood glucose monitoring and various prophylactic measures. For patients at higher risk of developing gastritis (ie, those taking nonsteroidal anti-inflammatory drugs [NSAIDS] or anticoagulants), histamine 2 (H2) blockers or proton pump inhibitors can be given during steroid therapy. Consider prophylactic antimicrobial and antifungal agents. Prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) should be considered in patients receiving a prednisone equivalent of ≥20 mg/day for 4 or more weeks, with general prophylaxis against fungal infections (ie, fluconazole) for patients receiving a prednisone equivalent of ≥20 mg/day for 6 or more

weeks. Consider prophylaxis against zoster reactivation. Lastly, vitamin D and calcium supplementation is recommended to reduce the risk of osteoporosis.

Anti-TNF-α therapy may pose a risk of reactivating viral infections such as viral hepatitis or tuberculosis (TB).[163-166] The panel recommends testing for hepatitis B and C virus prior to TNF inhibition, and carriers should be monitored during and for several months after immunosuppressive therapy. Additionally, testing for latent/active TB is recommended prior to initiation of infliximab therapy; IFN-gamma release assays are preferred. However, TB testing should not delay initiation of anti-TNFα agents for the management of acute severe or refractory irAEs.

Impact of Immunosuppressive Agents on Immunotherapy Efficacy

Although no prospective data exist, retrospective data generally suggest that immunosuppressive therapy initiated after onset of irAEs does not appear to decrease ICI efficacy. Results were recently published from a pooled analysis of 4 studies enrolling 576 patients who received nivolumab for advanced melanoma.[167] When adjusting for the number of nivolumab doses, ORR was higher among patients who experienced all-grade irAEs compared with those who did not. Among the 474 phase III trial participants, 114 (24%) received systemic corticosteroids for managing irAEs. ORR was not significantly different between patients who required corticosteroids and those who did not.[167] Similar findings were reported by an earlier retrospective analysis of 298 patients with metastatic melanoma who were treated with ipilimumab.[124] Within this cohort, 103 (35%) required corticosteroid therapy to manage irAEs, and 29 of these patients (10%) also required anti-TNF alpha therapy to address unresolved symptoms. OS and TTF were not impacted by the development of irAEs or the need for corticosteroid therapy to manage them.[124] Similarly, among a pooled group of 409 patients who received nivolumab plus ipilimumab combination therapy as part of CheckMate 067 and 069, ORR was not reduced among patients who required corticosteroid therapy to manage irAEs relative to the rest of the cohort.[87,168]

Investigators have also analyzed whether immunosuppression via TNF antagonist had a negative impact on combination ICI therapy response. Based on retrospective analysis of data from CheckMate 067 and 069, using infliximab to manage colitis did not appear to alter the kinetics of tumor response or durability.[87] Another analysis of pooled data from these trials demonstrated similar survival outcomes between patients with GI irAEs who received corticosteroid therapy ± infliximab and patients with GI irAEs who did not receive immunosuppressive agents.[168]

Due to clinical trial exclusion criteria, less is known about the impact of immunosuppressants on ICI efficacy when given prior to ICI therapy. A recent retrospective study identified 90 individuals who were on baseline corticosteroid therapy (≥10 prednisone equivalent daily) from a cohort of 640 patients with NSCLC on anti-PD-1/PD-L1 monotherapy. Baseline corticosteroid therapy was associated with poorer outcomes from ICI therapy, as indicated by decreased ORR, progression-free survival (PFS), and OS.[169] Additional research will be needed to better understand the potential impact of corticosteroid exposure prior to or during ICI therapy initiation, especially as it pertains to premedication with corticosteroid prior to ICI infusion.

Managing irAEs in Special Patient Populations

Patients with Prior irAEs or Pre-existing Autoimmune Conditions

In patients with pre-existing autoimmune disease, exacerbation of autoimmunity is a concern with the administration of immune-activating agents. Similarly, ICI therapy must be approached cautiously among patients who have experienced a prior irAE while receiving immunotherapy. Data on the toxicity of ICIs in patients with preexisting

autoimmune disease or irAEs is generally lacking due to exclusion of these populations from clinical trials leading to FDA approval. Based on limited data from smaller retrospective studies, ICIs appear to be similarly effective in these patient groups with response rates of 20% to 40%.[170-172] Based on the available data, most autoimmune disease flares and irAEs in this patient population have been managed with corticosteroid or additional immunosuppressive therapy; however, fatal AEs have been reported.[173] Preliminary data on safety and toxicity are described below.

In the largest series to date, ipilimumab therapy was provided to a cohort of 30 patients with advanced melanoma and pre-existing autoimmune disorders including inflammatory bowel disease (n = 6), rheumatoid arthritis (n = 6), psoriasis (n = 5), systemic lupus erythematosus (n = 2), multiple sclerosis (n = 2), autoimmune thyroiditis (n = 2), and various others.[172] Thirteen of 30 patients were taking immunosuppressive therapy to manage their conditions. While on ipilimumab, 27% of patients experienced exacerbation of their autoimmune condition, typically in the form of recurrent or enhanced preexisting symptoms. Most were managed successfully using corticosteroid, with 2 patients requiring infliximab. Ten patients (33%) experienced conventional high-grade irAEs considered unrelated to their baseline autoimmune condition (including one fatality due to colitis in a patient with skin-limited psoriasis). Three patients experienced concurrent autoimmune condition flares and conventional irAEs requiring high-dose corticosteroid. However, half of the cohort experienced no irAEs or autoimmune condition flare.[172]

Studies have also examined the effects of PD-1 inhibitors for advanced melanoma in patients with pre-existing autoimmune disease.[170,171] Among a subset of 19 patients with prior autoimmune disease, PD-1 inhibition led to autoimmune flare in 42%, and onset of a new irAE in 16%.[170] In a separate study of 52 patients with significant autoimmune conditions (eg, rheumatoid arthritis, polymyalgia rheumatica, Sjögren's syndrome, immune thrombocytopenic purpura, psoriasis), 38% had an autoimmune condition flare requiring immunosuppression, and 29% developed a new irAE.[171] Interestingly, no members of that cohort with GI or neurologic autoimmune conditions (n = 11) experienced a flare.[171] In both studies of PD-1 inhibitors, most flares of preexisting autoimmune conditions were adequately managed using immunosuppressive and symptomatic therapy.[170,171] However, onset of new irAEs led to discontinuation of PD-1 inhibitor in about 10% of patients in one study.[171]

Reviews of the data have also probed the impact of PD-1 inhibitor therapy for treating melanoma in patients who developed prior treatment-related irAEs during ipilimumab monotherapy or combination CTLA-4/PD-1 blockade.[170,171,174] Among the 22 patients with ipilimumab-related irAEs described by Gutzmer et al, treatment with a PD-1 inhibitor led to a flare of the prior irAE in 4.5% of patients, while 23% developed a new irAE. In another study of 67 patients with prior ipilimumab-related irAEs requiring immunosuppression, flare was reported in 3% of patients, and 34% developed new irAEs.[171]

Nivolumab or pembrolizumab monotherapy was resumed in a cohort of 80 patients who had previously discontinued combination ICI therapy due to irAEs.[174] Upon resumption of PD-1 inhibitor, 14 patients (18%) experienced a recurrence of the same irAE and 17 patients (21%) experienced clinically significant "distinct" or de novo irAEs. Half of the cohort (n = 40) experienced any-grade irAE, with high-grade toxicity in 18% (n = 14). Twenty-four patients (30%) discontinued PD-1 monotherapy due to irAE. Colitis and neurologic toxicities were found to be least likely to recur, whereas hepatitis, pancreatitis, nephritis, and pneumonitis recurred more commonly. Symptomatic hypophysitis and rash were assessed as intermediate risk for recurrence; however, 1 fatality occurred due to recurrent and worsening rash and bullous disease. Due to the relatively high rate of severe but distinct irAEs that were observed during anti-PD-1

agent rechallenge (21%), the authors posited two potential explanations. First, patients could be predisposed to subsequent toxicity due to immune priming by ICI combination therapy, and second, delayed presentation of irAEs due to combination therapy-related toxicity could have occurred.[174] Additional research is needed to understand the safety of ICI therapy in this population and others at a potentially greater risk for developing irAEs.

NCCN Recommendations

Optimization of immunosuppression for pre-existing autoimmune conditions and close cooperation with pertinent subspecialists is recommended. These guidelines suggest a goal of immunosuppressive regimen allowing for prednisone dose of <10 mg daily (or equivalent) prior to initiating cancer immunotherapy. However, patients with autoimmune neurologic conditions or life-threatening autoimmune disorders are unlikely to be suitable candidates for ICI immunotherapy. Additionally, ICI therapy may not be appropriate for patients whose autoimmune conditions are inadequately controlled using immunosuppressive medications, or for those who require high doses of immunosuppressive agents to manage their condition.

Caution should be exercised when considering resumption of ICI therapy for patients who have experienced a previous treatment-related irAE. A key consideration is the patient's tumor response. In patients with responding or stable disease, it may be prudent to continue close surveillance and to re-introduce ICI therapy if the patient develops evidence of progression of cancer. As appropriate, consult with organ-specific specialists prior to resumption. With some exceptions, resumption of ICI therapy after a grade 2 irAE can be considered once signs and symptoms have resolved to grade 1 or below. Perform close follow-up to monitor for any signs or symptoms of irAE recurrence. If toxicity returns upon ICI rechallenge, permanently discontinue that class of ICI.

In the setting of most severe (and some moderate) irAEs, permanent discontinuation of that given class of immunotherapy is typically warranted. For example, if a patient experiences grade 3 or 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with anti-PD-1/PD-L1 monotherapy upon full resolution of any earlier toxicity.

Organ Transplant Recipients

Concerns regarding graft rejection in transplant recipients has led to the exclusion of this patient population from many clinical trials of ICI therapy.[175] Safety and efficacy data on ICI therapy in patients who have received a prior organ transplant are limited to a small number of case reports. Safe ipilimumab use has been reported in several patients who received kidney or liver transplants.[175-178] A 2017 review of 12 case reports on ICI use in transplant recipients identified 4 patients who experienced kidney graft rejection after combination CTLA-4/PD-1 blockade or anti-PD-1 monotherapy.[175] PD-1 inhibition appears to be more commonly associated with graft rejection, suggesting that this pathway may play a more critical role in allograft immune tolerance.[175,179] Other factors to consider in organ transplant recipients who may be candidates for ICI therapy may include elapsed time between transplant and initiation of immunotherapy, the strength of maintenance immunosuppressive therapy required to prevent graft rejection, and the immunogenicity of the transplanted organ.[175,176]

Research is underway to explore alternative immunosuppressive regimens in an effort to reduce allograft rejection during ICI therapy.[176,179] The safety and utility of immunotherapy is also being investigated in patients with multiple myeloma who may be unable to mount an adequate immune response. In KEYNOTE 183 and KEYNOTE 185, more deaths were observed for treatment arms in which pembrolizumab was added to lenalidomide/dexamethasone or pomalidomide/dexamethasone.[180]

NCCN Recommendations

Consideration of ICI therapy in organ transplant recipients is very complex and requires multidisciplinary involvement. Graft failure while on ICI immunotherapy has been reported, and transplant organ loss may be an outcome of treatment. Patients with solid organ transplantation who have a viable option for alternative therapy if graft rejection occurs (ie, kidney and dialysis) may be candidates for immunotherapy, particularly if there is no prior evidence of graft rejection and patients are on a stable maintenance immunosuppression regimen. The possible consequences of ICI therapy should be discussed with the patient and organ transplant team and there should be a plan in place to seamlessly manage the patient if graft loss occurs. Although patients with prior allogeneic stem cell transplant may be candidates for immunotherapy, there is an increased risk of transplant-related complications, including potentially fatal graft-versus-host disease (GVHD). Careful discussion with the patient and stem cell transplant physicians should precede initiation of immunotherapy.

Specific irAE Management

In general, close consultation with disease-specific subspecialists is encouraged during irAE management. Referral to a tertiary care center may be required for management of complex cases or multi-system irAEs. Due to the kinetics of the immune response, the onset of irAEs can occur at any point during treatment or even after completion of therapy.[181,182] irAE rebound during steroid taper has also been reported. The typical timing and presentation of specific irAEs are discussed below. Please see the corresponding algorithm pages in the guidelines for detailed recommendations on assessing and treating particular irAEs by grade/severity.

Caution and careful judgment are required when considering whether to resume immunotherapy following significant toxicity. Clinicians should assess patient's tumor status prior to rechallenge. If an objective response (complete or partial) to ICI therapy was achieved, resumption of immunotherapy may not be advisable due to risk of toxicity recurrence. The NCCN Panel recommends that clinicians discuss the risks/benefits of restarting immunotherapy with the patient.

Infusion-Related Reactions

Infusion reactions have been reported most commonly with the PD-L1 inhibitor avelumab. Pooled safety data on avelumab reported that 25% of patients experienced any-grade infusion reactions (439/1738) with high-grade events in 0.7% (12/1738); the majority occurred during the first infusion, with nearly all reactions occurring within the first 4 treatment cycles.[28,183] Premedication appeared to decrease the rate of severe infusion-related reactions (IRRs).[183] The U.S. prescribing instructions for avelumab include acetaminophen and diphenhydramine prior to infusion during the first 4 treatment cycles.[28]

Most infusion reactions associated with ICIs are mild and associated with low-grade fever, chills, headache, or nausea. Severe or high-grade reactions occurred in <1% of patients across all other ICIs. Incidence of any-grade infusion reactions for the remaining ICIs include atezolizumab at 1.3%, durvalumab at 2.2%, <10% for PD-1 inhibitors, and <1% for ipilimumab monotherapy.[26,27,29-31,86]

NCCN Recommendations

The panel refers clinicians to the prescribing information for each individual immunotherapy agent for recommendations regarding premedication to prevent infusion reactions. In the absence of specific indications such as prior IRR or concurrent chemotherapy, routine premedication with corticosteroids prior to receiving ICI therapy is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.

In patients having a possible IRR, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform an ECG if the patient is experiencing chest pain or sustained tachycardia. Symptoms of IRRs can include fever, chills, rigors; urticaria/pruritus; angioedema; flushing; headache; hypertension or hypotension; and/or shortness of breath, cough, or wheezing. Hypoxemia, dizziness/syncope, sweating, and arthralgia or myalgia may also occur.

Mild (G1) reactions are typically transient and do not require immunotherapy infusion interruption or other intervention. For moderate (G2) reactions, hold or slow the rate of infusion and treat per institutional guidelines. Antihistamines, acetaminophen, NSAIDS, narcotics, or IV fluids may be required. Moderate reactions typically respond promptly to symptomatic treatment and require medication for ≤24 hours. Consider premedication with acetaminophen and diphenhydramine with future infusions. For severe (G3/4) IRRs, treat urgently according to institutional guidelines. Permanently discontinue the immune checkpoint drug(s) associated with the toxicity. Severe reactions are often more prolonged with limited responsiveness to intervention or infusion interruption. Symptoms can reoccur following initial improvement. Inpatient care and urgent intervention may be needed to prevent life-threatening consequences.

Dermatologic Toxicity

Dermatologic toxicities are the most prevalent irAEs associated with ICI therapy. Inflammatory skin conditions typically present within the first 2 cycles of treatment (ie, within several weeks).[60,93,96,184,185] Ipilimumab has been consistently associated with higher rates of all-grade dermatologic irAEs than PD-1/PD-L1 inhibitors; reported incidences of all grade dermatologic toxicity range from 37%–70% for ipilimumab and 17%–40% for PD-1/PD-L1 inhibitors. The rates of high-grade dermatologic irAEs are similar across ICI classes and range from 1%–3% for ipilimumab and PD-1/PD-L1 inhibitors.[85,93,186,187] Generally, regimens combining CTLA-4 blockade with an anti-PD-1/PD-L1 agent led to more frequent, severe, and earlier presentation of dermatologic toxicity.[188]

Maculopapular rash, with or without pruritus, is the most common presentation. Vitiligo is also a fairly common observation in patients with melanoma on PD-1 inhibitors, typically presenting later in the course of treatment. Observed inflammatory skin conditions reported with ICI therapy include eczematous, lichenoid, and psoriasiform manifestations, as well as bullous dermatitis.[60,184,188,189] Alopecia and hair repigmentation have also been reported.[188,190,191] The majority of dermatologic irAEs are low grade and manageable with appropriate care without requiring interruption of ICI. However, rare cases of severe cutaneous reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported.[189,192,193] Although serious conditions typically required hospitalization, resolution was achievable via systemic immunosuppressive therapy and ICI discontinuation.

<u>NCCN Recommendations</u>

To assess potential dermatologic irAEs, the guidelines recommend total body skin exam, including mucosa, and patient history of any prior inflammatory dermatologic disease. Routine examination of skin and mucosa is recommended for patients with a history of immune-related skin disorders. Clinicians should monitor the lesion type and affected body surface area (BSA); photographic documentation may be helpful. Biopsy can be considered for rash with unusual features. Treatment recommendations are subdivided by presentation. In general, short-term use of higher potency topical corticosteroids (eg, Class 2 or 3) is preferred over longer-term use of a lower-potency agent.

Maculopapular Rash

Maculopapular rash is characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and may be associated with pruritus. Oral antihistamine and topical emollient are recommended. Mild (G1) maculopapular rash should be treated with moderate-potency topical corticosteroid while ICI therapy continues. For moderate rash (G2), treatment with high-potency topical corticosteroids and/or 0.5–1 mg/kg/day prednisone is indicated. Consider holding immunotherapy. For severe rash (G3/4), hold immunotherapy and treat with high-potency topical corticosteroids and 0.5–1 mg/kg/day prednisone (with dose increase up to 2 mg/kg/day if no improvement). Urgent dermatology consultation is recommended; consider inpatient care. Following immunotherapy hold, consider resuming once symptoms have resolved to ≤ G1 and only topical interventions are indicated.

Pruritus

Pruritus is an intense itching sensation that may occur with or without rash. Mild pruritus (G1) can be treated with oral antihistamines and moderate-potency topical corticosteroid while immunotherapy is continued. Consult dermatology and continue immunotherapy with intensified antipruritic therapy for moderate pruritus (G2). Immunotherapy hold can be considered in select cases. Oral antihistamines are recommended in addition to high-potency topical steroid. For severe pruritus, hold immunotherapy and obtain urgent dermatology consultation. In addition to antihistamines, oral or IV prednisone/methylprednisolone (0.5–1 mg/kg/day) should be administered. Consider a GABA antagonist such as gabapentin or pregabalin, and aprepitant or omalizumab for refractory cases. Following immunotherapy hold, consider resuming once symptoms have resolved to ≤ G1 and only topical intervention is required.

Bullous Dermatitis and SJS/TEN

Bullous dermatitis and other forms of blistering skin reactions are characterized by skin inflammation and fluid-filled bullae. For mild to moderate bullous dermatitis, hold immunotherapy until resolution. High-potency topical corticosteroid (G1) or 0.5–1 mg/kg/day prednisone/methylprednisolone (G2) is indicated. For severe or life-threatening bullous dermatitis and all cases of SJS/TEN, hospitalization and permanent discontinuation of immunotherapy are required. Seek urgent consultation from dermatology, ophthalmology, and urology. Methylprednisolone/prednisone should be initiated at 1–2 mg/kg/day.

In cases for which systemic corticosteroid is indicated, treatment should be continued until symptoms improve to ≤ G1, followed by dose taper over 4 to 6 weeks.

Lichen Planus and Lichenoid Diseases

ICI-related lichen planus and lichenoid disease are characterized by violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, and significant pruritus.[194,195] Erosions and striae (white lines intersecting) in the oral and vulvar mucosa may also occur.[194,196] The mean time to onset is approximately 6 to 12 weeks after initiation of ICI treatment.[194] Up to 6% of patients who received ICI treatment have been reported to experience lichen planus or lichenoid disease.[197]

A single-center retrospective cohort study characterized the management of ICI-related lichenoid eruptions in 119 patients with various types of cancers.[196] Patients included 108 with lichenoid dermatitis, 15 with lichenoid mucositis, and 2 with lichenoid dermatoses. Topical steroids were the most frequently used treatments for the management of lichenoid dermatitis (81%). Other treatments included

oral antihistamines, oral steroids, acitretin, intralesional triamcinolone, narrow-band ultraviolet B (UVB), and other unspecified nonsteroidal treatment. Treatments used for lichenoid mucositis included topical steroids, unspecified nonsteroidal treatments, oral steroids, and acitretin.

Another single-center retrospective study assessed lichenoid mucocutaneous eruptions in 20 patients with advanced cancer who received programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors.[195] Eruptions on the trunk, extremities, and/or mouth were reported. Topical steroids were used most frequently, although some patients were also treated with oral steroids or phototherapy.

Other documented treatments used for lichen planus and lichenoid reactions (either ICI-related or idiopathic) included steroids (topical, intralesional, or oral), tacrolimus, narrow-band UVB phototherapy, cyclosporine, doxycycline, acitretin, apremilast, and other nonsteroidal immunomodulators such as hydroxychloroquine, azathioprine, methotrexate, and mycophenolate mofetil.[198-200]

High-potency topical steroids (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]) or tacrolimus (0.1% ointment) are recommended for all grades of lichen planus and lichenoid diseases. In general, gel can be considered for mucosal disease, solution for scalp disease, and cream/lotion/ointment for all other affected areas. Oral antihistamines, prednisone, and narrow-band UVB phototherapy (if available) are recommended for moderate lichen planus and lichenoid diseases. If severe, prednisone or intravenous (IV) methylprednisolone is recommended; other agents that can be considered include acitretin (if no childbearing potential), doxycycline in combination with nicotinamide, and other steroid-sparing immunosuppressants, such as azathioprine, cyclosporine, hydroxychloroquine, methotrexate, and mycophenolate mofetil. A referral to dermatology, if available, should also be considered for those with severe symptoms.

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

Psoriasis and Psoriasiform Diseases

ICI-related psoriasis and psoriasiform disease are characterized by thick, red, scaly plaques that are typically accentuated on extensor surfaces, scalp, umbilicus, and postauricular surfaces.[194,197,201] The time of onset is typically within 3 weeks of ICI treatment.[194] ICI-related psoriasis includes both *de novo* psoriasis and the exacerbation of existing psoriasis.[197,201]

A retrospective study characterized the treatments used for 115 patients with ICI-related psoriasis.[201] Over half of the patients presented with grade 1 psoriasis. Many patients were treated with only topical measures (59.1%), while 40.9% received both topical and systemic agents. Systemic therapies used included acitretin, systemic steroids, apremilast, methotrexate, and biologics specifically approved for psoriasis (eg, tumor necrosis factor [TNF]-alpha inhibitors, interleukin [IL]-23 inhibitors). Two patients received topical steroids in combination with narrow-band UVB phototherapy.

A separate systematic review of 60 published studies evaluated treatments used for the management of ICI-related psoriasis in 242 patients.[202] Topical steroids were the most common treatment used (83%). Other treatments included acitretin, systemic steroids, phototherapy, methotrexate, and biologics approved for psoriasis.

Systemic non-biologics recommended by the American Academy of Dermatology (AAD)/National Psoriasis Foundation (NPF) guidelines for idiopathic psoriasis include acitretin, apremilast, cyclosporine, methotrexate, and others.[203] AAD/NPF also recommend a number of approved biologics for the treatment of idiopathic psoriasis.[204] Of note, systemic steroids have historically not been used for the treatment of psoriasis due to risk of a pustular rebound flare and are not currently recommended by the AAD/NPF guidelines for the management of psoriasis.[201,203,205]

High-potency topical steroids (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]) and topical vitamin D analogues are recommended for all grades of ICI-related psoriasis and psoriasiform diseases. Narrow-band UVB phototherapy is recommended for moderate psoriasis, if available. Apremilast or acitretin (if no childbearing potential) can be considered if the irAE is deemed moderate or severe. Cyclosporine and methotrexate are recommended as additional treatment options for severe ICI-related psoriasis. The NCCN Panel also recommends referral to a dermatologist for consideration of biologics approved for the treatment of moderate or severe psoriasis.[204] Systemic steroids are not recommended for patients with ICI-related psoriasis/psoriasiform diseases.

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

Oral Mucosa Inflammation

Oral mucosa inflammation is characterized by irritated gums and/or oropharynx, including red/white lesions, erosions, and/or ulcers, striae, or diffuse mucositis. The prevalence of ICI-related oral mucosal disorders is estimated to be approximately 3%.[206]

Data on the treatment of ICI-related oral mucosa inflammation are limited. A retrospective single-center study evaluated 152 patients with various types of cancer who experienced ICI-related oral mucositis.[207] Grade 1 or 2 mucositis was reported in 91% of patients. Oral ulcers or aphthae were reported in 97% of patients. No medical treatment was given to 11% of patients and over half of patients were treated with only supportive medication, which consisted of viscous lidocaine, sucralfate, proton pump inhibitors (PPIs), and H2 blockers (also known as histamine H2 antagonists). The rest of the patients received topical and/or systemic immunosuppressants (23.7%), which included oral prednisone and IV methylprednisolone. None of the patients in the study received nonsteroidal systemic immunosuppressants.

A systematic review of published reports (primarily case studies) similarly identified topical measures and oral/IV steroids as the primary management strategies used to treat 42 patients with ICI-related oral mucositis.[208]

Good oral hygiene (such as twice-daily tooth brushing, chlorhexidine or fluoride oral rinse if tooth brushing is too painful) and dietary modifications (eg, avoidance of crunchy, spicy, or acidic foods; avoidance of hot food/drinks) are recommended by the NCCN Panel for all patients with oral mucosa inflammation. Referral to dermatology is recommended if available. A referral to dentistry should be considered for those with mild symptoms and strongly considered for those with moderate or severe inflammation to ensure adequate hygiene and to protect against the risk of dental caries. If available, a referral to an ear, nose, and throat (ENT) specialist is recommended to assist in the management of persistent mucositis or if there is oropharynx/larynx involvement.

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

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

Dry Mouth (Sicca Syndrome)

Dry mouth (also referred to as sicca syndrome) has been reported with ICI use.[209-211] Patients with sicca syndrome present with an abrupt onset of dry mouth that can cause difficulty with speaking, eating, swallowing, and/or staying asleep. Some patients, but not all, may experience dry eye.[211] Dry mouth (sicca syndrome) is estimated to occur in 2% to 11% of patients who receive ICI treatment.[206,209]

Data from a single-center study that included 20 patients who experienced ICI-related sicca syndrome showed that onset of the condition typically occurred within 3 months of treatment with ICIs.[210] Supportive care measures (including hydration and use of systemic sialagogues), steroids (eg, prednisone), and holding ICI therapy were the primary management strategies reported in the study.

Another study described management strategies based on ImmunoCancer International Registry (ICIR) data derived from 26 patients with various cancer types who developed sicca syndrome following ICI therapy.[211] Topical measures were initially used for most patients, while systemic steroids were administered to those for whom topical measures were ineffective. Use of other immunosuppressants in the second-line setting was also reported for select patients.

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

Oral Dysesthesia

Oral dysesthesia is generally described as oral pain with a "burning" sensation in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings. In the literature, multiple terms have been used to describe this condition, including burning mouth syndrome and stomatodynia.[212] This irAE is often not an isolated event and may occur with other types of ICI-related oral toxicities, such as mucosal inflammation. The prevalence of ICI-related oral/oropharyngeal pain is estimated to be 4%.[206]

Data on the management of ICI-related oral dysesthesia are limited. However, several studies have investigated treatment options for non-ICI–related oral dysesthesia. Data from a single-center study found that some, but not all, patients with burning mouth syndrome treated with steroids experienced an improvement in symptoms.[213] Use of gabapentin has been evaluated within the context of a randomized, double-blind, placebo-controlled trial in patients with symptoms of burning in the mouth.[214] Ten out of the 20 patients who received gabapentin alone experienced a reduction in burning sensation. Other topical agents, psychotropic medications, and psychological therapy have also been used to treat oral dysesthesia;[212,213] however, high-quality data are needed, especially within the context of ICI treatment.

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

Gastrointestinal (GI) Toxicity

GI irAEs may present as diarrhea or symptoms of colitis, which include watery diarrhea, cramping, and urgency. Diarrhea and colitis are the second-most commonly reported AEs with ICIs, and symptoms typically develop within 6 to 8 weeks of starting treatment.[215,216] GI irAEs have been reported more frequently with anti-CTLA-4 monotherapy than with PD-1/PD-L1 inhibitors. In studies of CTLA-4 blockade, diarrhea has been reported in up to half of patients, with incidence typically reported between 30% and 40%.[85,217] The highest rates of ICI-mediated GI irAEs have been observed with the addition of a PD-1/PD-L1 inhibitor to CTLA-4 blockade.[218-220] Retrospective case reviews suggest that symptom grade may not correlate with colitis severity as observed by endoscopy and histology.[121,221]

Systematic reviews and meta-analyses have examined the incidence of specific GI irAEs in patients with solid tumors who received ICI therapy. A meta-analysis of 34 studies enrolling 8863 patients with solid tumors examined the incidence of GI irAEs with various ICIs.[220] The highest rates of GI irAEs were observed in patients receiving combination ipilimumab plus nivolumab, with all-grade colitis, severe colitis, and severe diarrhea reported in 13.6%, 9.4%, and 9.2% of patients, respectively. Incidence of irAEs with ipilimumab monotherapy was 9.1% for all-grade colitis, 6.8% for severe colitis, and 7.9% for severe diarrhea. Monotherapy with a PD-1/PD-L1 inhibitor had the lowest GI irAE incidence, with 1.3% for all-grade colitis, 0.9% for severe colitis, and 1.2% for severe diarrhea. No significant differences in GI irAE incidence were observed by tumor type (eg, melanoma, NSCLC, RCC).[220] Another meta-analysis compared the pooled incidence of diarrhea and colitis for different checkpoint inhibitors in patients with melanoma (CTLA-4: n = 3116; PD-1 inhibitors: n = 1537). PD-1 inhibitors were associated with a lower relative risk of all-grade diarrhea and colitis compared with anti–CTLA-4 agents, while combination therapy was associated with a higher relative risk of diarrhea and colitis than monotherapy. Rates of discontinuation were higher among patients taking anti–CTLA-4 agents.[219]

Corticosteroids are typically the first line of treatment for GI irAEs. In retrospective reviews of patients with ICI-related enterocolitis, symptoms resolved with corticosteroid treatment in approximately 40% to 60% of individuals.[216,221,222] However, a recent retrospective analysis of patients found higher infection rates among patients treated with long-duration

steroids (>30 days). Long-duration corticosteroid without infliximab was associated with increased infection risk compared to short-duration steroid plus infliximab, suggesting that earlier non-steroid immunosuppressive therapy may confer better outcomes.[121]

Endoscopy revealed colonic ulcerations more commonly in steroid-refractory cases.[216,221,222] Case studies report on the successful use of infliximab for treating severe, steroid-refractory colitis associated with ipilimumab.[222-224] Case series and reports have also documented successful treatment of ICI-mediated, steroid-dependent, or steroid-refractory enterocolitis with vedolizumab.[131,225] Vedolizumab may be effective in the setting of infliximab-resistant inflammation of the small intestine and colon.[132]

NCCN Recommendations

Determine the patient's baseline bowel habits. Blood in the stools and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding. For patients presenting with mild diarrhea (G1), close monitoring is recommended with progressive symptoms indicating further workup. Loperamide or diphenoxylate/atropine and hydration are recommended, and consider holding immunotherapy. Moderate (G2) or severe (G3/4) diarrhea and colitis require stool evaluation to rule out infectious etiology. Consider abdominal/pelvic CT with contrast and GI consultation for further evaluation (ie, colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy [EGD] with biopsy). Therapy for irAE can be initiated while awaiting test results.

For moderate diarrhea/colitis (G2), hold immunotherapy and administer prednisone/methylprednisolone (1 mg/kg/day). If no improvement is noted within 2 to 3 days, increase corticosteroid dose to 2 mg/kg/day and consider adding infliximab. Consider inpatient care if needed to provide adequate supportive care for severe colitis (G3/4). Administer IV methylprednisolone, 2 mg/kg/day. If no response is detected in 2 days, continue steroids and consider adding infliximab. Consider vedolizumab for infliximab-refractory diarrhea and colitis or cases for which infliximab is contraindicated.

For patients taking ipilimumab, the panel recommends permanent discontinuation if a serious or life-threatening GI irAE occurs. For patients receiving PD-1/PD-L1 inhibitors, therapy should be held for G2/3 irAEs, with consideration of rechallenge upon resolution of symptoms below G1. For rare circumstances in which the patient cannot completely taper off corticosteroids, immunotherapy may be resumed while the patient is still on ≤10 mg prednisone (or equivalent) daily. Permanently discontinue the immunotherapy agent(s) responsible for the toxicity after G4 irAEs. If a systemic corticosteroid is given, treatment should be continued until symptoms improve to ≤ G1, followed by dose taper over 4 to 6 weeks. Convert from IV methylprednisolone to oral prednisone when appropriate.

Hepatic Toxicity

Although immune-related hepatotoxicity occurs at a lower rate than diarrhea/colitis, it is a well-documented ICI-mediated irAE that is typically mild but can be severe or even fatal in rare cases.[74] Asymptomatic elevations in aspartate transaminase (AST) and alanine transaminase (ALT) are the most commonly observed hepatic AEs.[66,186] The pooled incidence of immune-related hepatotoxicity is estimated at 3% to 9% for ipilimumab and between 0.7% and 1.8% for PD-1/PD-L1 inhibitors.[226] Combination therapy is associated with a considerably higher incidence of hepatotoxicity with 29% and 17% experiencing any-grade and high-grade hepatotoxicity, respectively.[226,227] Median time of onset is typically 5 to 6 weeks from start of treatment but irAEs can occur months later.[226,228-230] Autoimmune hepatitis and drug-induced hepatitis can present in a similar fashion and be difficult to distinguish, but can often be differentiated by distinct histologic features and imaging.[231,232] A recent study characterized

the distinct histologic patterns associated with hepatitis mediated by CTLA-4 versus PD-1/PD-L1 blockade.[228]

Corticosteroids are the most common method of treatment in most studies of ICI-mediated hepatotoxicity.[226,228,229] In several cases, re-initiation of steroids after taper was needed based on worsening liver values.[229] Mycophenolate has been used to treat severe persistent hepatitis despite corticosteroid therapy.[146,226,233,234] Another study reported the use of cyclosporine as an additional immunosuppressant in the setting of steroid-refractory hepatotoxicity.[229] Infliximab is not recommended given concerns for liver toxicity, although it has not been tested in this setting. Case report data also suggest that tacrolimus may be effective for treating refractory ICI-related hepatitis.[235,236]

NCCN Recommendations

Liver damage may be indicated by elevated levels of the liver enzymes ALT and AST (ie, transaminitis). Patients experiencing hepatic irAEs may present with varying grades of transaminitis. The panel recommends ruling out other potential factors such as viral etiology, disease-related hepatic dysfunction, or drug-induced enzyme elevations. Specialist consultation should be considered and efforts should be made to limit or discontinue any hepatotoxic medications. Assess acetaminophen, dietary supplement, and alcohol use.

Treatment recommendations are separated based on the co-occurrence of elevated bilirubin. Management of transaminitis without elevated bilirubin is by grade, based on the degree to which enzymes exceed the upper limit of normal [ULN]). For mild transaminitis (G1), immunotherapy can be continued with increased frequency of transaminase and bilirubin monitoring. Consider holding immunotherapy for concerning laboratory value trends. Hold immunotherapy for moderate transaminitis (G2) and monitor liver function tests (LFTs) every 3 to 5 days and consider prednisone 0.5–1 mg/kg/day. Severe or life-threatening transaminitis (G3/4) requires permanent discontinuation of ICI therapy, hepatology consult, and LFT monitoring every 1 to 2 days. Provide inpatient care for G4 transaminitis and consider hospitalization for G3. Liver biopsy can be considered if there are no contraindications. Initiate prednisone at 1–2 mg/kg/day (G3) or 2 mg/kg/day (G4). For patients with persistent severe hepatitis despite high-dose corticosteroid for 3 days, consider adding MMF. Infliximab is not currently recommended for use in patients with hepatitis.

For ≥ G2 transaminitis with bilirubin levels above 1.5 ULN (excluding patients with Gilbert's syndrome), management is similar to that for high-grade hepatitis without bilirubin elevation. Permanently discontinue immunotherapy and initiate prednisone at 2 mg/kg/day. Monitor LFTs daily and consult with hepatology. Mycophenolate can be considered in addition to steroid for refractory cases after 3 days.

For all hepatitis cases requiring corticosteroid, initiate tapering when liver enzymes show sustained improvement or return to ≤ G1. Continue to taper dose over at least 1 month with re-escalation as needed for rebounding enzyme levels. In the setting of G2 hepatis without elevated bilirubin, clinicians can consider resuming immunotherapy once liver enzymes return to baseline and prednisone (or equivalent) has been tapered to ≤10 mg daily. Do not rechallenge following high-grade (G3/4) irAEs.

Pancreatic Toxicity

Amylase and/or lipase elevations, although typically asymptomatic, can occur with ICI therapy. The potential significance of asymptomatic elevations remains unclear, but discontinuation of therapy is not usually recommended based on these findings alone.[85,186,237] Although rare, acute pancreatitis has been observed in patients taking ICIs,[186,231,238] and radiologic features of immune-related pancreatitis have been described.[239] Cases of recurrent pancreatitis have been reported upon resumption of

PD-1 inhibitors following a hold for initial irAE.[174] Toxic effects on the endocrine pancreas, such as hyperglycemia and diabetes, are addressed in the larger context of the endocrine system in the next section.

NCCN Recommendations

Baseline/routine amylase/lipase assessments and pancreatic imaging do not need to be performed outside of clinical suspicion of pancreatitis. For persistent moderate/severe elevations in amylase and/or lipase, the panel recommends evaluation for pancreatitis to include clinical assessment and imaging. Imaging may include abdominal CT with contrast or magnetic resonance cholangiopancreatography (MRCP). Other potential causes for elevated pancreatic enzymes should be considered. For moderate/severe elevations in amylase and/or lipase, consider continuing immunotherapy if no evidence of pancreatitis is found.

Provide standard medical care for signs and symptoms of acute pancreatitis, including hospital admission, aggressive fluid resuscitation, and pain control. Gastroenterology consultation and immunosuppression are warranted if clinical assessment and/or imaging findings support moderate/severe acute pancreatitis. For moderate (G2) pancreatitis, hold immunotherapy and initiate methylprednisolone/prednisone at 0.5 to 1 mg/kg/day. Permanently discontinue ICI therapy for severe (G3/4) pancreatitis and administer corticosteroid at 1–2 mg/kg/day.

In cases for which systemic corticosteroid is indicated, treatment should be continued until symptoms improve to ≤ G1, followed by dose taper over 4 to 6 weeks. If there is no evidence clinical/radiologic evidence of pancreatitis and amylase/lipase levels improve, clinicians can consider resuming immunotherapy after a hold for a symptomatic G2 irAE. Consider consulting with a pancreatic specialist regarding rechallenge. Resumption of immunotherapy is not recommended after G3/4 pancreatitis.

Endocrine Toxicity

ICI-related endocrine gland autoimmunity has resulted in dysfunction of the thyroid, pituitary, adrenal glands, and pancreas. Manifestations of immune-mediated endocrine gland dysfunction include hypothyroidism, hyperthyroidism, hypophysitis, type I diabetes, and primary adrenal insufficiency. The mechanisms of ICI-mediated endocrinopathies have been reviewed by Sznol et al and Byun et al.[240,241] Because many symptoms of endocrine toxicity could be related to other acute illnesses or underlying malignancy, diagnosis can be challenging. Additionally, clinicians have to differentiate whether the source of endocrine dysfunction is central (ie, pituitary) or primary (eg, adrenal or thyroid) in order to tailor management appropriately.[240,241] Due to this potential complexity, endocrinology specialists play an important role in the management of these irAEs, particularly for severe or complex cases. Alessandrino et al have reviewed imaging features of endocrine irAEs at presentation and after treatment to assist in making a differential diagnosis.[242]

Different patterns of endocrine dysfunction have been observed with various ICI regimens. Hypophysitis is characteristic of ipilimumab, while thyroid dysfunction is seen more commonly with PD-1/PD-L1 inhibitors. Other types of endocrine irAEs such as primary adrenal insufficiency and type I diabetes are considerably more rare. Overall, combination ICI therapy was associated with highest incidence of endocrinopathy.[86,240,241,243] Median time to onset of moderate to severe endocrinopathy has ranged between 1.75 and 5 months for ipilimumab. Median time to onset of endocrinopathy with PD-1 inhibitor monotherapy ranged from 1.4 to 4.9 months.[215,241]

A 2018 meta-analysis examined the incidence of endocrine dysfunction across 38 randomized trials enrolling 7551 patients who received monotherapy with PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor; or combination anti-PD-1/CTLA-4 therapy.[243] The estimated incidence of

hypothyroidism was 3.8% with ipilimumab and up to 13.2% for combination therapy. Compared with ipilimumab, PD-1 inhibitors were associated with a significantly greater risk of hypothyroidism (OR, 1.89; 95% CI, 1.17–3.05; $P = .03$). Interestingly, the risk of hyperthyroidism was higher with PD-1 versus PD-L1 inhibitors (OR, 5.36; 95% CI, 2.04–14.08; $P = .002$). Overall, the observed incidence of hypophysitis was 6.4% for combination therapy; 3.2% for CTLA-4 inhibitors; 0.4% for PD-1 inhibitors; and below 0.1% for PD-L1 inhibitors. Compared to PD-1 monotherapy, hypophysitis was a more common occurrence during ipilimumab monotherapy (OR, 0.29; 95% CI, 0.18–0.49; $P < .001$) and combination therapy (OR, 2.2; 95% CI, 1.39–3.60; $P = .001$). The rarer nature of primary adrenal insufficiency and diabetes precluded statistical comparison of endocrine irAE incidence between different ICI regimens.[243]

A retrospective review identified 27 cases of new-onset insulin- dependent diabetes from a population of 2960 patients that received ICI therapy over 6 years at 2 academic medical centers (0.9% prevalence).[244] All patients who developed or experienced a worsening of diabetes (ie, becoming insulin dependent) had received anti-PD-1/PD-L1 therapy. Median time to onset was 20 weeks after the first ICI cycle; 59% presented with ketoacidosis, 42% had evidence of pancreatitis, and 40% had one or more positive autoantibodies on testing. Additional concurrent irAEs were present among 70% of the individuals with ICI-related diabetes, many of whom experienced other endocrine AEs. Seventy-six percent of the individuals who developed ICI-related diabetes had the HLA-DR4 genotype, a significantly higher frequency than that reported for the general population, suggesting a possible high-risk allele for the development of this irAE.[244] However, further research will be needed.

ICI-mediated endocrine toxicity often results in permanent organ damage and typically requires life-long hormonal supplementation.[241,245-247] To date, evidence does not suggest that high-dose corticosteroid therapy mitigates organ damage in most cases of ICI-mediated endocrinopathy; however, corticosteroids may help to mitigate symptoms of acute inflammation in the setting of hypophysitis, adrenalitis, or in some cases, thyrotoxicosis. Experts generally do not recommend corticosteroid therapy for managing hypothyroidism or type I diabetes.[240,241,245,247,248]

NCCN Recommendations

Thyroid Dysfunction

Thyroid function should be assessed by monitoring the levels of thyroid-stimulating hormone (TSH) and free thyroxine (T4). In the setting of thyroid abnormalities, routine monitoring is recommended every 4 to 6 weeks. This interval can be extended to every 12 to 18 weeks in patients who have normal thyroid function or who continue to be asymptomatic. Evaluation of total T3 is recommended in the setting of abnormal findings.

For asymptomatic or subclinical hypothyroidism, defined as elevated TSH with normal free T4, continue routine monitoring and proceed with immunotherapy. Levothyroxine can be considered for TSH levels above 10 mIU/L. Primary hypothyroidism is characterized by elevated TSH levels (>10 mIU/L) and low free T4 with clinical symptoms. Provide thyroid supplementation and consider endocrine consultation. Prior to starting thyroid replacement therapy, concomitant adrenal insufficiency should be ruled out by testing AM cortisol levels. Low or suppressed TSH with inappropriately low free T4 may present as a sequela of hypophysitis, in which other pituitary axes may be affected. Follow free T4 for thyroid replacement in the setting of hypophysitis-induced loss of TSH production.

Although rare, thyroiditis (often a painless, transient inflammatory process) can occur with ICI therapy. Thyrotoxicosis, observed as low or suppressed TSH (<0.01 mIU/L) with high free T4 and/or total triiodothyronine (T3), may be symptomatic in the setting of high free T4. If symptomatic (eg, palpitations, anxiety, insomnia), consider endocrine consultation and propranolol to manage symptoms until resolution. Thyrotoxicosis often

evolves to hypothyroidism. Repeat thyroid function testing should be performed in 4 to 6 weeks. Findings of persistent suppressed TSH with high free T4/total T3 should be followed by additional testing for true hyperthyroidism and Graves' disease-like etiology. Hypothyroidism usually ensues after an occurrence of ICI-induced thyrotoxicosis. If TSH becomes significantly elevated (>10 mIU/L), thyroid supplementation should be initiated.

Immunotherapy may be continued in the setting of hypothyroidism or thyrotoxicosis. When appropriate, levothyroxine is given for thyroid hormone supplementation at approximately 1.6 mcg/kg with the intent of getting TSH levels to reference range or age-appropriate values. Levothyroxine dose can be reduced by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (ie, elderly or patients with comorbidities). The guidelines recommend TSH and T4 monitoring every 4 to 6 weeks during immunotherapy, with follow-up every 12 weeks thereafter, as indicated.

Hypophysitis

Acute symptoms of hypophysitis can include headache, photophobia, dizziness, nausea/emesis, fevers, anorexia, visual field cuts, or severe fatigue. Chronic symptoms can include fatigue and weight loss. Workup for hypophysitis should include assessment of adrenocorticotropic hormone (ACTH), AM cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), TSH, free T4, testosterone in men, and estrogen in premenopausal women. Test results indicative of hypophysitis may show low levels of the following: ACTH, AM cortisol, sodium, potassium, testosterone, and DHEA-S. If the patient is symptomatic, a brain MRI with pituitary/sellar cuts is recommended.

Consider consulting endocrinology if a diagnosis of hypophysitis is made. For acute, symptomatic hypophysitis (headache and symptoms that are caused by acute swelling of the pituitary), hold immunotherapy and initiate methylprednisolone/prednisone at 1–2 mg/kg/day until acute symptoms resolve, typically 1 to 2 weeks. Then taper steroids rapidly to physiologic replacement levels upon improvement. Consider resumption of ICI therapy once symptoms related to mass effect have resolved.

The more common presentation for hypophysitis features deficiency of TSH/ACTH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling. Patients may manifest a variety of symptoms related to deficiency of endogenous thyroid hormone, cortisol, or gonadal hormones. Immunotherapy can be continued while endocrine therapy is titrated to appropriate physiologic levels.

Physiologic hormone replacement will likely be required indefinitely (typically life-long), and should include steroid replacement, levothyroxine if accompanied by central hypothyroidism, and testosterone supplementation in males. Provide patient education regarding stress doses of hydrocortisone in the event of infection, trauma, or other medical event. Patients should wear a medical alert bracelet.

Primary Adrenal Insufficiency

Workup for primary adrenal insufficiency should include serum cortisol, as well as a comprehensive metabolic panel (CMP) and renin levels. Follow-up evaluation for abnormal findings should include ACTH, LH, FSH, and testosterone. Hallmarks of adrenal damage include low AM cortisol (<5) with ACTH above the reference range, with or without abnormal electrolytes and symptoms. Other abnormalities may include hypotension, orthostatic hypotension, low sodium, and high potassium.

Endocrinology should be consulted for these patients, with specialist evaluation prior to any surgery or procedure. Hold immunotherapy. If patients are hemodynamically unstable, inpatient care and high-dose/stress-dose corticosteroids are recommended. Patients with severe symptoms including hypotension may require additional fluids. It is

important to initiate corticosteroid replacement prior to other hormone replacement to avoid adrenal crisis. Steroid replacement will include hydrocortisone or prednisone, plus mineralocorticoid replacement (fludrocortisone). Immunotherapy can be resumed once endocrine replacement therapy has been established.

Physiologic hormone replacement will likely be required indefinitely (typically life-long). The goal for physiologic steroid replacement is to identify the lowest steroid dose needed to prevent symptoms of adrenal insufficiency. Provide patient education regarding stress doses of hydrocortisone in case of infection, trauma, or other medical event. Patients should wear a medical alert bracelet.

Hyperglycemia/Diabetes

Fasting glucose is preferred to assess potential hyperglycemia. Note that high-dose corticosteroids can induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if patients are symptomatic or hyperglycemia remains persistently uncontrolled. Management is guided by patient history of type II diabetes mellitus (T2DM), glucose levels, and concern for diabetic ketoacidosis (DKA). Symptoms of DKA may include excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath.

For patients with new-onset hyperglycemia less than 200 mg/dL, and/or a history of T2DM with low suspicion for DKA, the observed hyperglycemia may be corticosteroid-related or due to preexisting diabetes. Immunotherapy can be continued with serial blood glucose monitoring at each dose. Diet and lifestyle modifications are recommended as needed along with medical therapy per institutional guidelines.

Further workup is warranted for findings of 1) new-onset hyperglycemia >200 mg/dL; 2) random blood glucose >250 mg/dL; or 3) history of T2DM with glucose levels >250 m/dL. If any of the previous findings are noted, consider new-onset type I diabetes mellitus (T1DM) and evaluate for DKA. ICI-related development of T1DM is rare (1%–2%) but can be life-threatening if insulin therapy is not provided. Management and monitoring should be directed by endocrinology team. DKA requires hospitalization and immunotherapy hold. Management of DKA varies by institution and may include (but is not limited to) IV fluids with or without potassium supplementation, IV insulin, and hourly testing of glucose, serum ketones, blood pH, and anion gap. Corticosteroid therapy is not recommended for treating T1DM as there is insufficient evidence to suggest that it effectively reverses ICI-related T1DM, and it may further complicate glycemic control.

Pulmonary Toxicity

Pneumonitis has been associated with ICI therapy. Generally, rates of any-grade pneumonitis for PD-1/PD-L1 monotherapy have been reported at or below 5% for all-grade, and around 1% for high-grade pneumonitis.[249,250] Unlike the pattern with most other irAEs, ipilimumab monotherapy has a lower incidence of pneumonitis compared with PD-1/PD-L1 inhibitors, with reported rates of less than 1%.[251,252] Observed rates for combination immunotherapy (PD-1/PD-L1 inhibitor plus anti-CTLA-4) are higher than for monotherapy with other ICIs.[249,250,253] Although wide-ranging, median time to irAE onset from start of treatment has been reported at 2.5 months, with generally earlier onset for combination versus monotherapy.[249,253]

A 2016 meta-analysis of 20 clinical trials of PD-1 inhibitors that enrolled 4496 patients with melanoma, lung, or renal cancer revealed an overall incidence of all-grade and high-grade pneumonitis of 2.7% and 0.8%, with a higher incidence in NSCLC than melanoma.[250] Incidence was higher for combination therapy than for monotherapy (all-grade 6.6% vs. 1.6%, $P < .001$; high-grade 1.5% vs. 0.2%, $P = .001$).

A pooled analysis of 916 patients analyzed pneumonitis among patients who received PD-1/PD-L1 inhibitors with or without anti–CTLA-4 therapy. Incidence of pneumonitis for PD-1/PD-L1 inhibitor monotherapy versus combination therapy (PD-1/PD-L1 inhibitor + CTLA-4 inhibitor) was 3% versus 10%, respectively (*P* = .001). No significant differences were observed in rates of pneumonitis between PD-1 and PD-L1 inhibitors. A similar incidence of pneumonitis was observed among the largest disease cohorts, melanoma and NSCLC, for both monotherapy and combination therapy. Of the patients diagnosed with pneumonitis in this study, most low-grade cases were treated in the outpatient setting, but 19% of patients with G2 pneumonitis and all patients ≥G3 required inpatient care. All mild pneumonitis (G1) cases were managed using ICI dose holds or oral corticosteroid, while all moderate and severe cases received oral or IV corticosteroid. Among patients with G3 or higher pneumonitis, 42% required additional immunosuppression with infliximab alone or infliximab with cyclophosphamide.[249]

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These guidelines characterize mild pneumonitis (G1) as asymptomatic, confined to less than 25% of the lung parenchyma or a single lobe. Moderate pneumonitis (G2) is characterized by the presence of new or worsening symptoms including shortness of breath, cough, chest pain, and fever. Severe pneumonitis (G3) involves all lobes of the lung or greater than 50% of the lung parenchyma. The symptoms typically limit self-care activities of daily living (ADLs). Life-threatening (G4) pneumonitis involves serious respiratory compromise.

Baseline pulmonary function should be determined by measuring oxygen saturation (at rest and with ambulation), and pulmonary function tests are recommended for high-risk patients. Repeat oxygen saturation tests as symptoms indicate and evaluate for pneumonitis via chest CT. Pneumonitis can present as focal or diffuse inflammation of the lung parenchyma and is typically identified on CT imaging as ground-glass opacities. For mild to moderate pneumonitis (G1), consider holding immunotherapy and obtain chest CT, with repeat imaging in 4 weeks or sooner if clinically indicated for worsening symptoms. For mild pneumonitis, reassess in 1 to 2 weeks, including physical exam and pulse oximetry at rest and with ambulation. For moderate pneumonitis (G2), consult pulmonology and order infectious workup to include nasal swab for potential viral pathogens as well as sputum, blood, and urine cultures. The panel recommends infectious evaluation with institutional immunocompromised panel. Bronchoscopy with bronchoalveolar lavage (BAL) can be used to rule out infection and malignant lung infiltration. Consider chest CT with repeat imaging in 3 to 4 weeks. Consider empiric antibiotics if infection has not yet been fully excluded and begin methylprednisone/prednisolone at 1–2 mg/kg/day. Monitor every 3 to 7 days with physical examination and pulse oximetry. Treat with corticosteroid until symptoms improve to ≤ G1 and then taper over 4 to 6 weeks. The panel recommends treating per the algorithm for severe (G3) pneumonitis if no improvement is seen after 48 to 72 hours of corticosteroid therapy.

Permanently discontinue immunotherapy for all cases of severe or life-threatening pneumonitis. Inpatient care is required. Complete infectious workup and bronchoscopy with BAL as per the G2 algorithm and consult with pulmonology and infectious disease specialists. Consider empiric antibiotics if infection has not yet been fully excluded and begin methylprednisone/prednisolone at 1–2 mg/kg/day. Assess response within 48 hours and plan a slow corticosteroid taper over ≥6 weeks. If no improvement is observed after 48 hours of treatment, consider additional immunosuppression with any of the following agents: infliximab, MMF, or IVIG.

Resumption of immunotherapy following mild pneumonitis can be considered upon radiographic evidence of improvement. Following G2 irAE, rechallenge can be considered upon resolution of pneumonitis to ≤ G1 and no requirement for steroid.

Renal Toxicity

Based on initial studies, the estimated incidence of all-grade renal toxicity is approximately 2% for monotherapy, and up to 4.9% for ICI combination therapy.[227,254] Based on a review of phase II and III clinical trials of ICIs enrolling 3695 patients, the incidence of high-grade renal toxicity was 0.6%.[254] However, reviews of emerging data suggest that incidence of renal toxicity could be considerably higher.[255,256] For ipilimumab, time to onset of renal toxicity has been reported to be around 6 to 12 weeks for ipilimumab, but 3 to 12 months for PD-1 inhibitors.[257]

In the largest case series to date, time to onset of renal toxicity was around 3 months from initiation of ICI therapy, but varied from 3 weeks to approximately 8 months.[254] Within the cohort of 13 patients, kidney injury was preceded by an extrarenal irAE in 7 patients and pyuria (>5 white blood cells [WBC] per high-power field [HPF]) was present in 8 of 13 patients. Pathology revealed acute tubulointerstitial nephritis in 12 of 13 patients. Among the 10 patients who were treated with corticosteroid, 9 patients showed recovery of renal function (complete recovery in 2, partial recovery in 7). Four patients required hemodialysis, and 2 remained dialysis-dependent.[254] Other case reports/series have discussed similar approaches to diagnosis and management of ICI-related nephritis.[258-260] Notably, there is conflicting evidence surrounding the efficacy of corticosteroid therapy for treating acute interstitial nephritis linked to non-ICI–related causes.[261,262]

<u>NCCN Recommendations</u>

Elevated serum creatinine could indicate a developing renal irAE. Signs of acute renal failure may include azotemia, creatinine elevation, and ability to maintain acid/base or electrolyte balance, and changes in urine output. Mild renal irAEs (G1) are categorized by serum creatinine levels 1.5 to 2 times above baseline or an increase in ≥0.3 mg/dL. Creatinine levels of 2 to 3 times above baseline are considered moderate renal irAEs (G2). With severe irAEs (G3), creatinine levels may be in excess of 3 times above baseline, or >4.0 mg/dL. Creatinine levels >6 times above baseline indicate life-threatening renal issues (G4) and necessitate dialysis.

Upon development of signs of acute renal damage, the panel recommends conducting a medication review and limiting/discontinuing any nephrotoxic medications (eg, NSAIDS). Dose adjust remaining medications to creatinine clearance. Evaluate for and rule out other potential alternative etiologies for abnormal findings, testing as indicated for potential prerenal and postrenal causes (eg, contrast-enhanced imaging). Distinguish cell infiltrate from immune-complex–mediated injury. Possible considerations should include cardiomyopathy, heart failure, pulmonary hypertension, kidney stones/obstruction, hypovolemia due to a primary GI issue, diuretics, and infection. Protein-to-creatinine ratio in spot urine samples can be used to assess proteinuria, with follow-up testing for findings of proteinuria above 3 g/24-hour (ie, ANA, RF, ANCA, anti-dsDNA, serum C3 and C4, CH50).

For mild to moderate renal irAEs (G1), follow creatinine and urine protein every 3 to 7 days. Consider holding immunotherapy for G1 renal dysfunction, and hold immunotherapy dose in the setting of moderate renal irAEs (G2). If other causes are ruled out, administer prednisone 0.5–1 mg/kg/day. Increase dose to 1–2 mg/kg/day of methylprednisone/prednisolone for persistent G2 issues beyond 1 week. After G1/2 irAEs, once symptoms resolve to ≤ G1, consider resuming immunotherapy concomitant with corticosteroid.

Permanently discontinue immunotherapy if severe/life-threatening renal irAEs occur. Consider inpatient care, consult nephrology and consider

renal biopsy, and initiate methylprednisone/prednisolone at 1–2 mg/kg/day. For persistent findings above G2 after 1 week of steroid therapy, consider adding one of the following agents: azathioprine, monthly cyclophosphamide, cyclosporine, infliximab, or mycophenolate.

When corticosteroid therapy is used to manage renal irAEs, continue until improvement to ≤ G1, then taper over 4 to 6 weeks.

Ocular Toxicity

Ophthalmic irAEs are categorized by the affected area of the eye, into ocular inflammation (eg, uveitis, episcleritis, blepharitis, peripheral ulcerative keratitis), orbital inflammation/orbitopathy (eg, idiopathic or thyroid-induced orbitopathy), retinal/choroidal disease (eg, retinopathy or choroidal neovascularization), and optic neuropathy.[263-265] Dry eye and uveitis have been the most commonly reported ocular ICI-associated events, with a reported incidence between 1% and 24%.[265-267] Based on case series and reports, mild ophthalmic irAEs have generally been managed successfully using a topical steroid, whereas more severe conditions have required systemic corticosteroid therapy and discontinuation of ICI therapy.[264,265,268,269] Close cooperation with ophthalmologic specialists is critical for prompt diagnosis and optimal treatment.[264,267]

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Signs or symptoms such as blurred/distorted vision, changes in color vision, blind spots, photophobia, eye pain, eyelid swelling, and proptosis may indicate the development of an ocular irAE such as uveitis, episcleritis, or blepharitis. Episcleritis can be associated with red/purple discoloration of the eye, and uveitis may present with eye redness. Grading for uveitis is broken out by mild uveitis (G1), anterior uveitis (G2), posterior or panuveitis (G3), and uveitis causing vision of 20/200 or worse (G4). Episcleritis is graded as mild (G1), associated with vision of 20/40 or better (G2), associated with vision of 20/40 or worse (G3), or associated with vision of 20/200 or worse (G4).

For mild uveitis, episcleritis, or blepharitis, continue immunotherapy, provide artificial tears, and refer to ophthalmology. Avoid eye irritants such as contact lenses and cosmetics. Hold immunotherapy for G2 ocular irAEs and seek urgent ophthalmology consultation. Permanently discontinue immunotherapy for any G3 or G4 ocular irAEs and obtain emergent ophthalmology consultation. Treatment for moderate to severe irAEs should be guided by ophthalmology and will likely include ophthalmic and systemic prednisone/methylprednisone. For ophthalmic conditions refractory to high-dose systemic corticosteroid, consider adding infliximab or an antimetabolic agent (eg, methotrexate).

Corticosteroid treatment should be continued until resolution to ≤ G1, followed by dose taper over 4 to 6 weeks. For G2 ocular irAEs, the panel suggests consideration of resuming immunotherapy in consultation with ophthalmology upon resolution of the irAE to ≤ G1. Rechallenge is contraindicated after high-grade irAEs.

Nervous System Toxicity

ICI-mediated neurologic toxicity spans a broad spectrum of conditions related to autoimmunity within the central and/or peripheral nervous systems. Some neurologic irAEs can be quite challenging to diagnose due to nonspecific symptoms, variability in presentation, and the wide range of differential diagnoses to consider.[154,156,270] Documented cases of neurologic irAEs include numerous conditions such as myasthenia gravis, GBS-like syndrome, central and/or peripheral neuropathy, aseptic meningitis, encephalitis, and transverse myelitis. With some exceptions (eg, peripheral neuropathies), irAEs of the nervous system are higher grade events by default. Fatalities have been reported in patients receiving ICI who developed severe neurologic irAEs such as immune-mediated encephalitis, myasthenia gravis/myasthenic syndromes, and acute

immune demyelinating polyneuropathy.[154,155,270-274] The neurologic irAEs that most commonly resulted in fatality were encephalitis and myasthenia gravis.[101]

A systematic review of the literature examined data on neurologic AEs from case reports and prospective ICI trials (59 trials, n = 9208).[275] The overall incidence of neurologic irAEs was 3.8% for CTLA-4 inhibitors, 6% with PD-1 inhibitors, and 12% for combination therapy. Headache, encephalopathy, and meningitis were the most commonly reported events; the majority of events were lower grade.[275] Generally, reviews report a ≤1% incidence of high-grade neurologic irAEs across various ICI regimens.[156,273,275] Another study probed a pharmaceutical Global Pharmacovigilance and Epidemiology database for neurologic irAEs reported in patients with advanced melanoma receiving nivolumab with or without ipilimumab (12 trials, n = 3763).[156] Out of 3763 patients, 35 (0.93%) experienced 43 serious neurologic irAEs over an 8-year period, with neuropathy being the most commonly reported event. Resolution of irAE(s) was documented in 75% of patients (26 of 35).

Literature and database reviews generally report a median time to onset of neurologic irAEs of about 6 weeks.[154,156,275] Corticosteroid therapy is usually employed as the first line of treatment for neurologic irAEs; high-dose IV corticosteroids and ICI discontinuation was employed in the setting of higher-grade events.[154,156] Prompt treatment is critical for reducing long-term morbidity and mortality.[123,154,156,270,273] Median time to irAE resolution has been reported at just under 8 weeks.[156] Of note, unlike canonical cases of GBS, ICI-mediated development of GBS-like syndrome has been successfully managed using corticosteroid therapy.[275]

Additional lines of immunosuppressive therapy are often required for cases of rapidly progressive or steroid-refractory neurologic irAEs. Autoimmune encephalitis and other neurologic irAEs have been managed with agents such as IVIG, plasmapheresis, rituximab, and cyclosporine, leading to partial or full recovery.[154,156,272] However, for several reported cases of myasthenic syndrome, encephalitis, or demyelinating polyneuropathy, irAEs proved fatal despite treatment with multiple lines of immunosuppressant (including plasmapheresis, IVIG, tacrolimus, and/or MMF).[154,155] At present, there are no definitive outcomes data to guide decisions regarding immune-modulating treatments, and clinicians have relied on data from neurologic irAE case reports, management of other autoimmune neurologic disorders, and individual patient characteristics (ie, the presence of irAEs affecting other organ systems).[154]

<u>NCCN Recommendations</u>

Myasthenia Gravis

If myasthenia gravis is suspected, obtain neurology consultation. Assessment should include pulmonary function testing, electromyography (EMG) and nerve conduction study, as well as consideration of brain and/or spine MRI if symptoms are suggestive of malignant CNS involvement. Laboratory testing should include acetylcholine receptor and muscle-specific tyrosine kinase antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine phosphokinase, and aldolase for possible superimposed myositis. If the patient has respiratory insufficiency or elevated CPK, perform cardiac examination to include ECG, troponin, and transthoracic echocardiogram for possible concomitant myocarditis.

Hold immunotherapy for moderate symptoms (G2) with some interference in ADLs. Administer pyridostigmine and gradually increase to a maximum of 120 mg orally four times/day as tolerated and based on symptoms. Consider low-dose oral prednisone at 20 mg daily and gradually increase to a target dose of 1 mg/kg/day (not to exceed 100 mg daily). Taper these agents based on symptom improvement. Consider resuming immunotherapy based on steroid responsiveness. Severe cases (G3/4) warrant permanent discontinuation of immunotherapy, hospitalization, and

neurology consultation with daily neurologic evaluation and frequent pulmonary function testing. Start methylprednisolone 1–2 mg/kg/day. For patients with refractory, severe, or worsening symptoms, initiate plasmapheresis or IVIG. Medications that can worsen this condition, such as beta-blockers, ciprofloxacin, and IV magnesium, should be avoided.

Guillain-Barré Syndrome (GBS)
Inpatient care with access to intensive care–level monitoring is recommended; consult neurology. Recommended testing includes spinal MRI, lumbar puncture, serum antibody testing for GBS variants, and pulmonary function testing. Permanently discontinue immunotherapy for all cases of GBS and provide inpatient care with capability for rapid transfer to ICU-level monitoring. Initiate IVIG or plasmapheresis in addition to pulse dose methylprednisolone (1 g/d for 5 days). Conduct frequent neurologic examinations and pulmonary function testing. Monitor for concurrent autonomic dysfunction and provide non-opioid analgesic for management of neuropathic pain.

Unlike classical GBS, in immune-mediated GBS, cerebrospinal fluid (CSF) findings often include elevated protein and WBC count. Although corticosteroid is not typically indicated in idiopathic GBS, a trial is reasonable if the suspected cause is ICI therapy. Slow steroid taper is recommended once symptoms resolve. Immunotherapy rechallenge is not recommended.

Peripheral Neuropathy
Evaluate for other potential causes when assessing mild to moderate peripheral neuropathy. Potential factors include medication, infection, metabolic or endocrine disorders, vascular or autoimmune disease, and trauma, among other potential causes. Any cranial nerve involvement should be treated as a G2 irAE. Gastrointestinal tract paresis due to myenteric neuritis is a rare toxicity associated with ICI therapy.[276] The presentation may be fulminant with profound ileus. Early institution of high-dose steroids in concert with multidisciplinary management is recommended.

In the setting of peripheral neuropathy, obtain neuraxial imaging as recommended by neurology. For mild cases, consider holding immunotherapy and continue to monitor symptoms for any new interference with ADLs due to pain, weakness, difficulty walking, ataxia, or autonomic changes. Hold immunotherapy for moderate cases (G2) and observe closely. If symptoms progress, initiate methylprednisolone/prednisone at 0.5–1 mg/kg/day and administer gabapentin, pregabalin, or duloxetine for pain. Increase dose to 2 to 4 mg/kg/day if further progression. Severe peripheral neuropathy (G3/4) is not necessarily GBS, but management can be similar. Gabapentin, pregabalin, or duloxetine can be administered for neuropathic pain.

Aseptic Meningitis
When assessing immunotherapy patients for meningitis, exclude potential infectious causes and consider neurology consultation. The panel recommends brain MRI (with and without contrast) to include the pituitary gland. ACTH and AM cortisol can be used to rule out adrenal insufficiency. Lumbar puncture may be helpful in making a differential diagnosis. Relevant measures include opening pressure, CSF cell counts, protein glucose, gram stain, and culture for infectious organisms. Findings may include elevated WBC count with normal glucose, culture, and gram stain. Reactive lymphocytes or histiocytes may be observed on cytology. Based on these results, conduct polymerase chain reaction (PCR) for herpes simplex virus or other suspected viral infections.

If severity is mild to moderate, hold immunotherapy. If severe (G3/4), provide inpatient care and permanently discontinue immunotherapy. IV acyclovir can be considered until PCR results are obtained. Once infectious etiology has been ruled out, closely monitor or initiate

corticosteroid therapy at 0.5–1 mg/kg/day. Provide methylprednisolone dose of 1–2 mg/kg/day for moderate to severe symptoms. Taper corticosteroid rapidly once symptoms resolve. Consider resuming immunotherapy following mild to moderate aseptic meningitis only if symptoms have completely resolved.

Encephalitis

Infectious causes of encephalitis should be excluded. Consult neurology and perform brain MRI (with and without contrast), lumbar puncture, and electroencephalography (EEG) to rule out seizure activity. Laboratory testing should include CMP, complete blood count (CBC), thyroid panel including thyroid peroxidase (TPO) and thyroglobulin, as well as autoimmune and paraneoplastic panels. Also test ESR, CRP, and antineutrophil cytoplasmic antibody if vasculitis process is suspected. MRI may reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis. CSF may have elevated WBCs with lymphocytic predominance and/or elevated protein.

Hold immunotherapy for mild cases (G1), but permanently discontinue if moderate or severe (G2/3/4) encephalitis occurs. Severe encephalitis warrants inpatient care. A trial of acyclovir can be initiated until CSF PCR results are obtained. Also consider a trial of methylprednisolone 1–2 mg/kg/day. If symptoms are severe/progressive, or if oligoclonal bands are present on CSF, consider pulse-dose corticosteroid (1 g/day for 3–5 days) in addition to IVIG. Consider rituximab if limited or no improvement is seen after 1 to 2 weeks and test results are indicative of autoimmune encephalopathy.

Transverse Myelitis

Consult with neurology. Recommended assessment includes MRI of the brain and spine, lumbar puncture, and evaluation for urinary retention or constipation. Examine CSF for cell counts, protein, glucose, oligoclonal bands, cytology, and onconeural antibodies, and conduct viral PCRs as indicated. Laboratory studies include B_{12} levels, HIV testing, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, TSH, and aquaporin-4 IgG and paraneoplastic panel. Inpatient care is recommended. Discontinue immunotherapy. Provide pulse-dose methylprednisolone (1 g/day for 3–5 days) and strongly consider IVIG or plasmapheresis.

Cardiovascular Toxicity

Cardiac irAEs are potentially fatal ICI-associated toxicities that have been associated with ipilimumab, pembrolizumab, and nivolumab. Case series reveal a variety of potential manifestations of cardiovascular irAEs, including myocarditis, cardiomyopathy, cardiac fibrosis, heart failure, and cardiac arrest.[76,277,278] Efforts to characterize cardiac irAEs associated with ICI therapy have begun to provide a better understanding of ICI-associated myocarditis. Data collected over 4 years from 8 sites revealed 35 cases of ICI-mediated myocarditis, which were compared to a sample of patients on ICI therapy without myocarditis.[278] Prevalence was 1.14% in this patient population with a median onset of 34 days from initiation of treatment. However, recent evidence suggests that ICI-associated cardiovascular toxicity, myocarditis in particular, is more common than initially thought.[101,278-280]

Recent analysis of the WHO database revealed 101 individual case safety reports of severe myocarditis following initiation of ICI therapy.[280] Of these cases, 57% had received anti PD-1 monotherapy, and 27% received combination PD-1/PD-L1 plus CTLA-4 inhibitor. For cases with available dosing information (n = 59), 64% (n = 38) had received only 1 or 2 ICI doses at the time of toxicity onset. Concurrent severe irAEs, most commonly myositis and myasthenia gravis, were reported for 42%. Data on cardiovascular comorbidities were not available, but only 25% were on a cardiovascular or diabetes medication regimen.[280]

Based on multicenter registry data, myocarditis was observed more often in patients receiving combination ICI therapy and in patients with diabetes.[278] Approximately half of the patients diagnosed with myocarditis experienced major adverse cardiac events (MACE), which were defined as "the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block."[278] Troponin levels of ≥1.5 ng/mL were associated with a 4-fold increased risk of MACE (HR, 4.0; 95% CI, 1.5–10.9; *P* = .003). Corticosteroid was administered in 89% of cases, with high-dose steroids resulting in better treatment response. Elevated troponin and higher rates of MACE were observed more commonly among patients who were treated with lower-dose corticosteroid.[278]

Pre-existing cardiovascular pathology was identified in the majority of patients (5/8) in one case series.[277] Co-occurrence with non-cardiac irAEs was also observed in over 50% of patients. Corticosteroids and/or supportive care measures were helpful to improve symptoms in most cases, although permanent cardiotoxicity and fatalities also occurred despite intervention.[277] Myositis and myocarditis were observed to co-occur in a recent study of ICI-related fatalities. Notably, myasthenia gravis also co-occurred in 10% of fatal myocarditis cases.[101] Case reports of ICI-related myocarditis have reported irAE flare during steroid taper or ICI rechallenge.[281,282] IVIG was successfully used in a case report of smoldering ICI-related myocarditis that initially responded to corticosteroid but flared upon taper.[281]

NCCN Recommendations

Immediate cardiology consultation and inpatient care is recommended. Assessment should include telemetry monitoring, ECG, and cardiac MRI. Recommended laboratory testing includes cardiac biomarkers (creatine kinase and troponin) and inflammatory biomarkers (ESR, CRP, and WBC count). Seek to rule out other potential causes via viral titers, echocardiogram, or biopsy in the case of severe symptoms.

In the setting of severe (G3) cardiac irAE, arrhythmia may be accompanied by significant echocardiogram findings without hypotension, and cardiac biomarkers above the ULN. Life-threatening (G4) cardiac irAEs are denoted by arrhythmia, hemodynamic instability, and cardiac biomarkers more than 3 times the ULN. Permanently discontinue immunotherapy for any G3 or G4 cardiovascular irAEs. The panel recommends methylprednisolone pulse dosing (1 g/day for 3–5 days). Treat until cardiac function returns to baseline, then dose taper over 4 to 6 weeks. For life-threatening cases (G4), if no improvement is noted within 24 hours, consider adding infliximab or anti-thymocyte globulin (ATG).

Musculoskeletal Toxicity

Musculoskeletal and rheumatic irAEs include IA, myositis, and myalgias. Myositis is characterized by inflammation involving the skeletal muscles, and myalgia involves marked discomfort originating from a muscle or group of muscles. IA is typically identified as a result of joint pain (arthralgia) and/or swelling and stiffness after inactivity. Although rare, severe myositis can be fatal and has been documented more commonly in patients receiving PD-1/PD-L1 inhibitor.[283]

A recent systematic review of the literature examined rheumatic and musculoskeletal irAEs associated with ICI therapy. Data from 33 clinical trials, 3 observational studies, and 16 case reports/series were included.[283] Arthralgia and myalgia were the most commonly reported irAEs, with a widely ranging incidence of 1% to 43%. Five of 33 clinical trials reported cases of arthritis development, and case reports have described IA, vasculitis, myositis, and lupus nephritis. Prospective cohort studies and retrospective reviews report the incidence of IA or other rheumatologic irAEs among patients receiving ICIs to be between 1% and 7%.[122,283-285]

Among a prospective cohort study of 524 patients receiving ICIs, 35 (6.6%) were referred to rheumatology.[122] Twenty patients had IA that presented similar to rheumatoid arthritis (n = 7), polymyalgia rheumatica (n = 11), or psoriatic arthritis (n = 2), while the remaining 15 patients were diagnosed with noninflammatory musculoskeletal conditions. Nineteen patients with IA required low to moderate doses of corticosteroid, and methotrexate was administered in 2 patients. Notably, ICI therapy was not discontinued in these cases.

One case series initially reported on 13 patients (5 receiving nivolumab or ipilimumab monotherapy, 8 receiving combination ICI) who developed new rheumatologic symptoms while receiving an ICI at an academic medical center between 2012 and 2016.[286] Clinical presentation varied, with involvement in both large and small joints of the upper and lower extremities. All patients were treated with corticosteroid therapy, demonstrating variable response. The authors later published their findings on the distinct clinical presentation of IA within a cumulative series of 30 patients who received various ICI regimens.[287] Patients who received PD-1/PD-L1 inhibitor monotherapy tended to have small joint IA as their sole irAE, whereas patients on a combination regimen (PD-1/CTLA-4 blockade) were more likely to present with knee arthritis, higher levels of CRP, and prior irAE of another type, and display a reactive arthritis-like phenotype. Ten of 30 patients required additional lines of immunosuppressive therapy beyond corticosteroid (ie, methotrexate or TNF blockers).[287]

Reported cases of IA or other rheumatologic irAEs have generally been responsive to immunosuppressive therapy, with approximately one-quarter to one-third of patients requiring additional lines of therapy beyond corticosteroid.[122,287,288]

<u>NCCN Recommendations</u>

Inflammatory Arthritis (IA)

When assessing for IA, note the number of joints involved, perform a functional assessment, and obtain imaging as appropriate (eg, x-ray, joint ultrasound, joint MRI). Continue immunotherapy if arthritis is mild and administer NSAIDS or low-dose corticosteroid for refractory symptoms. Intraarticular steroids can be considered depending on joint location and the number of involved joints. For moderately severe arthritis, consider holding immunotherapy and administer prednisone 0.5 mg/kg/day for 4 to 6 weeks. If no improvement is seen within a month, treat per the algorithm for severe IA and seek rheumatology consultation. For severe arthritis that limits instrumental ADLs (with or without irreversible joint damage), hold immunotherapy and prescribe methylprednisolone/prednisone 1 mg/kg/day. If no improvement by week 2, consult rheumatology for consideration of additional disease modifying anti-rheumatic drugs depending on the clinical phenotype of inflammatory arthritis. Consider the co-existence of other irAEs in which choice of immunosuppression may be relevant; options may include infliximab, methotrexate, tocilizumab, sulfasalazine, azathioprine, leflunomide, and IVIG. Continued lack of improvement warrants rheumatology consultation for consideration of additional disease-modifying anti-rheumatic agents such as sulfasalazine, methotrexate, or leflunomide.

Continue to treat IA with corticosteroid until symptoms improve to a mild level, then taper the dose over 4 to 6 weeks. Perform serial rheumatologic examinations to monitor the patient's condition; if levels were initially elevated, ESR and CRP testing can also be used to monitor treatment response. After an immunotherapy hold, clinicians can consider resuming therapy upon stabilization or adequate management of symptoms. However, severe IA that impairs ADLs and quality of life may require permanent discontinuation of immunotherapy.

Myositis/Myalgia (Muscle Weakness)

Order a CMP and check creatine kinase and aldolase levels during workup for myositis or myalgia. Immunotherapy can continue uninterrupted in the setting of mild pain. Continue serial creatine kinase/aldolase monitoring and treat pain as indicated. For moderate, severe, or life-threatening (ie, myositis only, urgent intervention required) irAEs, obtain muscle MRI and EMG. Administer prednisone 1–2 mg/kg/day and treat pain as appropriate. Hold immunotherapy if creatine kinase/aldolase levels are elevated. Muscle biopsy can be considered for severe or refractory cases. Creatine kinase/aldolase serial monitoring should continue until symptoms resolve or corticosteroid has been discontinued. Corticosteroid treatment should continue until symptoms are ≤ G1, followed by dose taper over 4 to 6 weeks. Consult rheumatology for follow-up as well as neurology for myositis.

Hematologic Toxicity

This section is under development.

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