Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events

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Abstract: Immune checkpoint inhibitors (ICPIs), in the form of monoclonal antibodies against CTLA-4, PD-1, and PD-L1, have dramatically changed the treatment approach in several advanced cancers. Due to their mechanism of action, these novel agents are associated with a unique spectrum of immune-mediated adverse events (imAEs), with a safety profile that indicates they are better tolerated than traditional chemotherapeutic agents. This article aims to provide education on the current knowledge about imAEs associated with ICPI treatment, including strategies and tools for the prompt identification, evaluation, and optimal management of these events. The identification and management of imAEs are reviewed based on published literature, labeling guidelines, and the authors’ personal experience with patients. The imAE safety profiles of ICPIs vary, depending on the specific antibody and the type of cancer being treated. Although most imAEs are mild and easily managed, early identification and proactive treatment are essential actions serving both to reduce the risk of developing severe imAEs and to maximize the potential for patients to receive the benefits of ongoing ICPI treatment. As a primary point of contact for patients undergoing oncology treatment, nurses play a critical role in identifying imAEs, educating patients about the importance of timely reporting of potentially relevant symptoms, and assisting in the treatment and follow-up of patients who develop imAEs while on ICPI therapy.

Keywords: immune-mediated adverse event, checkpoint inhibitor, immunotherapy, CTLA-4, PD-1, PD-L1

Introduction

Harnessing the power of a patient’s immune system to attack cancer cells has become a reality. In recent years, immune checkpoint inhibitors (ICPIs) have emerged as a new class of drugs capable of augmenting the body’s immune response against several different tumor types.1–21 ICPIs approved by the US Food and Drug Administration (FDA) include monoclonal antibodies against CTLA-4 (ipilimumab22), PD-1 (nivolumab,23 pembrolizumab24), and, most recently, PD-L1 (atezolizumab,25 avelumab,26 and durvalumab27). Additional indications are being explored for approved agents,28–34 and other ICPIs are in late-stage development, including a new anti-CTLA-4 antibody (tremelimumab; Table 1).35 Furthermore, combination anti-CTLA-4 and anti-PD-L1 antibody therapy (ipilimumab + nivolumab) was recently added to the National Comprehensive Cancer Network Guidelines as a second-line treatment for small cell lung cancer,36 and many combinations are in development.

ICPIs are monoclonal antibodies targeting CTLA-4, PD-1, or PD-L1, checkpoint proteins known to prevent excessive immune response. ICPIs can influence the body’s
immune response against tumor cells by revitalizing suppressed immune cells, hence promoting an antitumor immune response. CTLA-4 and PD-1/PD-L1 are nonredundant T-cell activation checkpoint pathways, acting at different stages of the antitumor immune response. CTLA-4 is primarily involved in the early stages of T-cell activation within the

**Table 1** ICIs approved or in late-stage development

| Agent | Tumor type | ORR (%) | Approved (dose)/stage of development |
|-------|------------|---------|-------------------------------------|
| **Anti-CTLA-4 monotherapy** | | | |
| Ipilimumab | Melanoma – unresectable or metastatic (1L+) | 11<sup>21</sup>b | Approved<sup>22</sup> (3 mg/kg q3w, up to four doses) |
| | Melanoma with pathologic involvement of regional lymph nodes – adjuvant | 49<sup>21</sup>c | Approved<sup>22</sup> (10 mg/kg q3w, up to four doses, then q12w up to 3 years) |
| **Anti-PD-1 monotherapy** | | | |
| Nivolumab | Melanoma – unresectable or metastatic<sup>1</sup> | 1L BRAF wt | 34<sup>23</sup> |
| | | BRAF wt and BRAF mut+ | 40<sup>23</sup> |
| | 2L+ | 32<sup>23</sup> |
| | NSCLC – metastatic (2L) | Squamous | 20<sup>23</sup> |
| | | Nonsquamous | 19<sup>23</sup> |
| | Renal cell carcinoma – advanced (2L) | | 22<sup>23</sup> |
| | Urothelial carcinoma – locally advanced or metastatic (2L or 1L after neoadjuvant/adjuvant chemotherapy)<sup>6</sup> | | 20<sup>23</sup> |
| | HNSCC – recurrent or metastatic (2L) | | 13<sup>23</sup> |
| | Classical Hodgkin lymphoma – relapsed or refractory | 2L after HSCT and brentuximab vedotin therapy<sup>8</sup> | 66<sup>23</sup> |
| | | 4L+, including prior HSCT<sup>8</sup> | 69<sup>23</sup> |
| | Glioblastoma | | – |
| | HCC – advanced (1L) | | – |
| | Gastric cancer and gastroesophageal junction cancer – unresectable advanced or recurrent | | – |
| | SCLC – relapsed (2L) | | – |
| Pembrolizumab<sup>3</sup> | Melanoma – unresectable or metastatic<sup>1</sup> | 1L | 33<sup>24</sup> |
| | | Ipilimumab-refractory | 21<sup>24</sup> |
| | NSCLC (PD-L1+) – metastatic | 1L PD-L1+ (high levels) | 45<sup>24</sup> |
| | | 2L PD-L1+ | 18<sup>24</sup> |
| | HNSCC – recurrent or metastatic (2L)<sup>6</sup> | | 16<sup>24</sup> |
| | Urothelial carcinoma – locally advanced or metastatic<sup>6</sup> | 1L if cisplatin-ineligible<sup>6</sup> | 29<sup>24</sup> |
| | | 2L or 1L after neoadjuvant/ adjuvant chemotherapy | 21<sup>24</sup> |
| | Classical Hodgkin lymphoma – relapsed or refractory, regardless of prior HSCT or brentuximab vedotin therapy (4L)+<sup>8</sup> | | 69<sup>24</sup> |
| | | MSI-H or dMMR solid tumor – unresectable or metastatic (2L+) with no satisfactory alternative treatment options<sup>8</sup> | 40<sup>24</sup> |
| | | MSI-H or dMMR CRC – unresectable or metastatic (2L+, after treatment with fluoropyrimidine, oxaliplatin, and irinotecan)<sup>8</sup> | 36<sup>24</sup> |
| | TNBC – metastatic (2L and 3L) | | – |
| | Gastric/gastroesophageal junction adenocarcinoma – unresectable, locally advanced, or metastatic (2L) | | – |
| **Anti-PD-L1 monotherapy** | | | |
| Atezolizumab | Urothelial carcinoma – locally advanced or metastatic<sup>6</sup> | 1L if cisplatin-ineligible<sup>6</sup> | 24<sup>25</sup> |
| | | 2L or 1L after neoadjuvant/ adjuvant chemotherapy<sup>6</sup> | 15<sup>25</sup> |
| | NSCLC – metastatic (2L) | | 14<sup>1</sup>–15<sup>25</sup> |

(Continued)
lymph node, whereas the PD-1/PD-L1 pathway acts at late stages of the antitumor immune response within the tumor microenvironment. Therefore, targeting both checkpoints provides the potential for additive or synergistic effects.57,58

ICPIs have improved the prognosis for patients with advanced melanoma, BRAF^wt^ mutation-positive unresectable Stage III, locally advanced, or metastatic (1L and 3L) – Phase III: MYSTIC (NCT02453282), ARCTIC (NCT02352948)

Urothelial carcinoma – locally advanced or metastatic (2L or 1L after neoadjuvant/adjuvant chemotherapy) – Phase III: JAVELIN Lung 200 (NCT02395172)

Ovarian cancer – platinum resistant/refractory (2–4L) – Phase III: JAVELIN Ovarian 200 (NCT02580058)

Combination anti-CTLA-4 + anti-PD-1/PD-L1

| Agent | Tumor type | ORR (%) | Approved (dose/stage of development) |
|-------|------------|---------|-------------------------------------|
| Avelumab | Merkel cell carcinoma – metastatic | 33^26 | Approved^28 (10 mg/kg q2w) |
| | Urothelial carcinoma – locally advanced or metastatic (2L or 1L after neoadjuvant/adjuvant chemotherapy) | 13^26 | |
| | Gastric or gastroesophageal cancer – unresectable, locally advanced, or metastatic (3L) | – | Phase III: JAVELIN Gastric 300 (NCT02625623) |
| | NSCLC (PD-L1+) – locally advanced or metastatic (2L) | – | Phase III: JAVELIN Lung 200 (NCT02395172) |
| | Ovarian cancer – platinum resistant/refractory (2–4L) | – | Phase III: JAVELIN Ovarian 200 (NCT02580058) |
| Durvalumab | Urothelial carcinoma – locally advanced or metastatic (2L or 1L after neoadjuvant/adjuvant chemotherapy) | 17^27 | Approved^29 (10 mg/kg q2w) |
| | Urothelial carcinoma – unresectable (1L) | – | Phase III: DANUBE (NCT02516241) |
| | NSCLC – unresectable Stage III, locally advanced, or metastatic (1L and 3L) | – | Phase III: PACIFIC (NCT02125461), MYSTIC (NCT02453282), ARCTIC (NCT02352948) |
| | HNSCC – recurrent/metastatic (1L and 2L) | – | Phase III: KESTREL (NCT02551159), EAGLE (NCT02369874); FDA fast-track designation^104 |

Notes: *Late-stage development refers to Phase III sponsored studies that expect to have primary results on or before Q1 2018 in tumor types different from those in which the agents are already approved. ^Best overall response rate. ^Recurrence-free survival rate. ^Accelerated approval for BRAF V600 mutation-positive unresectable metastatic melanoma; continued approval may be contingent on confirmatory trials. ^Accelerated approval; continued approval may be contingent on confirmatory trials. Pembrolizumab is also approved in combination with pemetrexed and carboplatin as 1L treatment for metastatic nonsquamous NSCLC (ORR, 55%). ^Accelerated approval; continued approval may be contingent on confirmatory trials.

Abbreviations: 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; CRC, colorectal cancer; dMMR, mismatch repair-deficient; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; HSCT, hematopoietic stem cell transplant; ICPIs, immune checkpoint inhibitors; MSI-H, microsatellite instability-high cancer; NSCLC, non-small cell lung cancer; ORR, objective response rate; q2w, every 2 weeks; q3w, every 3 weeks; q12w, every 12 weeks; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; wt, wild type; mut, mutant; –, not available.

Due to their novel mechanism of action, ICPIs are associated with a spectrum of immune-mediated adverse events (imAEs) that differ from the typical adverse events seen with chemotherapeutic agents.57,48 By inhibiting the checkpoints for T-cell activation, ICPIs can cause the patient’s immune system to recognize and attack tumor cells. However, this deregulation of the immune system may also lead to immune-mediated toxicities, which can mimic a broad range of autoimmune conditions.49 By understanding the signs and symptoms of these unique adverse events, oncology nurses will be better equipped to educate, monitor, and manage cancer patients receiving ICPIs. This article reviews the imAE profile of anti-CTLA-4 and anti-PD-1/PD-L1 anti-
bodies, including an approach for monitoring patients and managing the imAEs associated with this new and growing therapeutic class.

**Dosing of ICPIs**

Dosage recommendations for ICPIs include both weight-based and fixed doses (Table 1).22–27 Although imAE risk appears to be greater with the higher dose of anti-CTLA-4 therapy (ipilimumab 10 mg/kg) than with the lower dose (ipilimumab 3 mg/kg),22 a similar dose effect on toxicity has not been observed in clinical studies of the currently marketed anti-PD-1 antibodies (nivolumab, pembrolizumab).50–53 Available safety data are based on registration studies that included varying dosing regimens for pembrolizumab (2 mg/kg or 10 mg/kg every 2 or 3 weeks)24 and weight-based dosing for nivolumab (3 mg/kg), which was the recommended dose until September 2016 when a 240 mg fixed dose was deemed to provide a similar drug exposure.23,53 Clinical registration studies of anti-PD-L1 antibodies utilized the current recommended doses (atezolizumab 1200 mg,25 avelumab 10 mg/kg,26 and durvalumab 10 mg/kg). Combination anti-CTLA-4 and anti-PD-1 therapy is currently dosed as same-day ipilimumab (3 mg/kg) followed by nivolumab (1 mg/kg) every 3 weeks for four doses, followed by nivolumab (240 mg) every 2 weeks thereafter.23 As this combination regimen is associated with greater toxicity than ICPI monotherapy,22–26 alternative dosing strategies are being evaluated in clinical studies with the objective of improving the safety/efficacy profile, including lower-dose anti-CTLA-4 antibodies in combination with anti-PD-1/anti-PD-L1 antibodies (nivolumab + ipilimumab,54 pembrolizumab + ipilimumab,55 durvalumab + tremelimumab56). Unlike chemotherapy where it is typical to dose-reduce patients to manage toxicities, the only dose modifications currently allowed with ICPIs are to either delay or discontinue therapy. Therefore, establishing the optimal dosing regimen of checkpoint inhibitors is very important.

**imAEs**

Typically, imAEs associated with ICPI treatment are low grade and manageable when identified promptly and treated properly.57,58 In clinical studies reporting the overall rate of imAEs, imAEs occurred in up to 90% of patients receiving ICPI monotherapy (Table 2).4,7,9,10,16–18,20,39,40,43,59,60 However, the incidence of high-grade (Grade ≥3) imAEs in these studies was generally much lower, especially with anti-PD-1 or PD-L1 antibodies. Notably, Grade ≥3 imAEs were reported to occur more frequently in patients receiving anti-CTLA-4 monotherapy (ipilimumab, 15–42%)4,9,39,40 than in those receiving anti-PD-1 (8%, nivolumab;4 5–10%, pembrolizumab16,20) or anti-PD-L1 (5–7%, atezolizumab;2,17 2%, durvalumab;59 1–2%, avelumab61) monotherapy, and the highest rate of Grade ≥3 imAEs was reported with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab, 40–45%).49 The skin and gastrointestinal tract are the most common sites for imAEs with any of the approved ICPIs, either in monotherapy or in combination, although any organ system can be affected (Table 3). In this section, we highlight the five most common organ systems affected by imAEs in patients treated with ICPIs: dermatologic, gastrointestinal, endocrine, hepatic, and pulmonary. Less common but clinically important manifestations of imAEs are also briefly reviewed (renal, pancreatic, ocular, musculoskeletal, neurological, cardiovascular, and hematological toxicities).

**Dermatologic**

Rash and pruritus are the most common dermatologic adverse events observed in patients receiving ICPI therapy, occurring more frequently with anti-CTLA-4 therapy (ipilimumab: 3 mg/kg [rash, 15–30%; pruritus, 24–35%],59,42 10 mg/kg [rash, 34%; pruritus, 40%]59) than with anti-PD-1 (nivolumab/pembrolizumab: rash, 4–22%; pruritus, 2–23%)2,4,10,13,17,59–61 or anti-PD-L1 treatment (atezolizumab/avelumab/durvalumab: rash, 1–7%; pruritus, 1–11%).7,10,13,17,59–61 Skin toxicities are typically low grade, often presenting as erythematous macules/papules/plaques on the trunk or extremities with or without pruritus during the early weeks of treatment (Figure 1).57,63,64 Dermatologic toxicities have been observed more often in patients receiving ICPIs for melanoma than for NSCLC (Table 2).2,4,6,9,11,13,16,41,43,50,51,65,66 Vitiligo may occur more frequently in patients receiving anti-PD-1 antibodies (nivolumab/pembrolizumab, 7–11%) than with anti-CTLA-4 therapy (ipilimumab, 2–4%).42 Grade 3/4 skin imAEs are rare, although cases of Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported in patients receiving anti-CTLA-4 (ipilimumab)2,23,57 or anti-PD-1 treatments (nivolumab/pembrolizumab).23,67

**Gastrointestinal**

Diarrhea is the most common gastrointestinal adverse event, occurring in 23–41% of patients treated with anti-CTLA-4 (ipilimumab: 3 mg/kg, 23–35%; 10 mg/kg, 41%),4,9,39,40,42 7–19% of patients treated with anti-PD-1 antibodies (nivolumab, 8–19%;4,6,11,13,16,41,62 pembrolizumab, 7–16%2,16,42,43,50,51), 2–15% of patients receiving anti-PD-L1 therapy (atezolizumab, 7–15%;7,13,17,44 avelumab, <1–9%;10,61
Table 2 Frequency of organ-specific imAEs in melanoma, NSCLC, and UC registration clinical trials

| Grade | Dermatologic, % | Gastrointestinal, % | Endocrine, % | Pulmonary, % | Renal, % | Neurologic, % |
|-------|-----------------|---------------------|-------------|-------------|---------|-------------|
| All   | All 44–63 0–3    | All 29–37 8–12     | All 8–15 2–4 | All 2 0–1   | All 2 0–1 | All 2 0–1   |
|       | 63 5 29–42 <1–2 | 46 16 12–20 1–2   | 38 9 7–14 0–1| 25 11 3–6 1–3| 2 16 11 0–1| 2 0–<1 0–1 |
|       | 59–73 6–9       | 46–49 15–20 8      | 30–31 5     | 30–32 13–19| 30–32 13–19| 2 0–<1 0–1 |
|       | 9 0 NR NR       | 8 1 NR NR          | 4 NR NR     | 2 0 NR NR  | 4 NR NR    | 0–1–2   |
|       | 17 1 1          | 9 2 NR NR          | 6–11 3–6    | 2 0 NR NR  | 4 2 2       | 1       |
|       | 1 1             | NR NR              | 0–1–2       | <1–1        | <1–1       | <1–1     |
|       | 1 0 NR NR       | 1 0 NR NR          | 1 0–1–2     | 4 2 NR NR  | 2 4 2       | 1–2–1   |
| All   | 5 0–1–1     | 5 1–2 1–2 1       | 1 0–1–2     | 1 0–1–2     | 1 0–1–2     | 1–2–1   |
|       | 1 0–1–2       | 1 0–1–2 1–2 1     | 1 0–1–2     | 1 0–1–2     | 1 0–1–2     | 1–2–1   |
| Pruritus | 24–35 0–<1 | 28–35 5–11 | 8–12 2–9 | 8–12 2–9 | 8–12 2–9 | 8–12 2–9 |
|       | 40 2 2–22 0–1 | 16 8 1–3 1–2 | 16 8 1–3 1–2 | 16 8 1–3 1–2 | 16 8 1–3 1–2 | 16 8 1–3 1–2 |
|       | 33–40 1–2     | 12–18 8–13 1–2   | 1–2 <1–2   | <1–1        | <1–1       | <1–1     |
|       | 2–10 NR NR     | 4–14 0–4 <1–1     | <1–1        | <1–1 <1–1   | <1–1       | <1–1     |
|       | 17–20 8–13     | 0–1–2              | <1–1         | 1–2–1       | 1–2–1     | 1–2–1   |
|       | 8–13 2         | 9–10               | 1–2          | 1–2          | 1–2       | 1–2     |
|       | 8–13 2         | 9–10               | 1–2          | 1–2          | 1–2       | 1–2     |
| NSCLC | Anti-PD-1 16,18,19,20,95 | 2 0–1 | 2 0–1 | 2 0–1 | 2 0–1 | 2 0–1 |
|       | Anti-PD-L 17,25,44 | 1–2 | 1–2 | 1–2 | 1–2 | 1–2 |
| Anti-CTLA-4 | 3 mg/kg | 3 mg/kg | 3 mg/kg | 3 mg/kg | 3 mg/kg | 3 mg/kg |
| Anti-PD-L | 1–2 | 1–2 | 1–2 | 1–2 | 1–2 | 1–2 |

Notes: Pivotal trials that led to US FDA approval. Pivotal trials that led to US FDA approval. Pivotal trials that led to US FDA approval. Pivotal trials that led to US FDA approval. Pivotal trials that led to US FDA approval. Pivotal trials that led to US FDA approval. Pivotal trials that led to US FDA approval. Pivotal trials that led to US FDA approval.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; FDA, Food and Drug Administration; imAEs, immune-mediated adverse events; NR, not reported; NSCLC, non-small cell lung cancer; UC, urothelial carcinoma.
### Table 3 Evaluation and management of imAEs

| Organ               | ImAE            | Symptoms                        | Evaluation                                                                 | Grading       | Management                                                                 |
|---------------------|-----------------|---------------------------------|-----------------------------------------------------------------------------|---------------|-----------------------------------------------------------------------------|
| Dermatologic        | Rash            | Maculopapular rash              | Rule out:                                                                   | Grade 1–2:    | Covers ≤30% of body surface area                                            |
|                     | Pruritus         | Pruritus                        | Cellulitis                                                                   | ±Pruritus      | Start topical steroid cream, anti-itch cream, oral antihistamine, cold compresses, oatmeal baths |
|                     | Erythema         | Hair color changes              | Contact dermatitis                                                          | Grade 3–4:    | If rash persists for >1 week or interferes with daily living, start moderate potency steroid cream |
|                     | Dry mouth        | Skin discoloration              | Drug reaction                                                                | ≤30% of body surface area ±Pruritus | Evaluate for desquamation, hold ICPI                                     |
|                     | Vitiligo (hair, skin) | Skin peeling, blisters          | Sun exposure                                                                 | Limits self-care ADLs | Refer to dermatologist, consider photoprotection                          |
|                     | Stevens–Johnson syndrome | Oral ulcerations | Radiation recall                                                             | Life-threatening consequences | Consider additional immunosuppressant (eg, infliximab)                     |
|                     | Toxic epidermal necrolysis | Eosinophil infiltrates           | Laboratory: CBC                                                             |               | Grade 4: Permanently discontinue ICPI                                     |
|                     |                  | Epidermal spongiosis            | Dermatology consult                                                          |               | Start steroid followed by tapering as for Grade 3                        |
|                     |                  | Lichenoid deposits              | Confirmatory testing: skin biopsy                                            |               | Grade 2: Hold ICPI until Grade 1                                        |
| Gastrointestinal    | Diarrhea         | Abdominal pain                  | Determine frequency and volume of stool                                      | Grade 1:      | If recurrent or if lasting >5 days, consider starting steroid dose (prednisone 1.0–2.0 mg/kg/day or equivalent) |
|                     | Colitis          | Cramping                        | Laboratory: CBC and CMP                                                     | <4 stools over baseline | Grade 2: 4–6 stools over baseline                                         |
|                     | Enterocolitis    | Change in bowel pattern         | Send stool sample for:                                                       | Asymptomatic   | If imAE resolves to Grade 1 or less, taper steroid dose over 4–6 weeks and consider resuming ICPI |
|                     | Nausea           | Increase in ostomy output       | WBC (ratio inflammation)                                                     | Grade 2: 6–12 stools over baseline | Grade 3: Hold MPS 1.0–2.0 mg/kg/day                                      |
|                     | Vomiting         | Mucous or blood in stool        | C&S and *Clostridium difficile*                                              | IV fluids <24 hours indicated | If imAE resolves to Grade 1 or less, taper steroid dose over 4–6 weeks and consider resuming ICPI |
|                     | Gastritis        | Intolerance                     | (ratio infection)                                                            | Colitis with abdominal pain, blood in stool, no ADL interference | Grade 4: Grade 4: Life-threatening perforation                             |
|                     | Ischemic gastritis | Peritoneal signs               | Diagnostic testing:                                                          | Grade 3: ≥7 stools/day over baseline | Grade 4: Grade 4: Life-threatening perforation                             |
|                     | GI perforation   |                                | Abdominal ultrasound                                                         | IV fluids >24 hours | Grade 4: Life-threatening perforation                                       |
|                     | Perforation sepsis |                                | Abdominal CT scan                                                            | Interference with ADLs | Grade 4: Life-threatening perforation                                       |
|                     | Ileus            |                                | Gastroenterology consult                                                     | Severe abdominal pain, peritoneal signs; medical intervention indicated | Grade 4: Life-threatening perforation                                       |
|                     |                  |                                | Confirmatory testing                                                        | Grade 4: Life-threatening perforation | Grade 4: Life-threatening perforation                                       |
|                     |                  |                                | Endoscopy                                                                    | Grade 4: Life-threatening perforation | Grade 4: Life-threatening perforation                                       |
|                     |                  |                                | Colonoscopy                                                                  | Grade 4: Life-threatening perforation | Grade 4: Life-threatening perforation                                       |
| Endocrine (thyroid) | Hyperthyroidism  | Weight loss/gain                | Laboratory: TSH, free T4 (thyroxine), free T3 (triiodothyronine)            | Grade 1:      | Grade 1: Continue ICPI                                                     |
|                     | Thyroiditis      | Feeling hot/cold                | Endocrinology consult                                                        | Asymptomatic   | Grade 2: Hold ICPI until Grade 1                                            |
|                     | Hypothyroidism   | Changes in mood/behavior        | T4 (thyroxine), T3 (triiodothyronine)                                       | Symptomatic    | Manage symptoms                                                             |
|                     |                  | Fatigue                         | Endocrinology consult                                                        | Requiring hormone replacement or medical intervention | Hyperthyroidism                                                            |
|                     |                  | Increased sweating              |                                                                             | Grade 3–4:     | Medical management for severe symptoms                                      |
|                     |                  | Faster/slower heart rate        |                                                                             | Severe symptoms, life-threatening | Hyperthyroidism                                                            |
|                     |                  | Diarrhea/constipation           |                                                                             | Requiring hospitalization or urgent medical intervention | Initiate hormone replacement if TSH >10                                      |
|                     |                  | Hair loss                       |                                                                             | Limiting self-care ADL | Adjust replacement hormone dosing to maintain T4 in mid-range             |
|                     |                  | Heat/cold intolerance           |                                                                             |               | Consider resuming ICPI when symptoms resolve to ≤Grade 1                   |

(Continued)
### Table 3 (Continued)

| Organ (HPA axis) | ImAE | Symptoms | Evaluation | Grading* | Management |
|------------------|------|----------|------------|----------|------------|
| **Endocrine**    |      |          |            |          |            |
| Hypophysitis     |      | Hypophysitis: visual changes, headaches, fatigue, weakness, confusion, hallucinations, memory loss, labile mood, insomnia, anorexia | Laboratory: CBC and blood cultures to rule out sepsis | Grade 1: | Continue ICPI |
| Adrenal insufficiency | Hypophysitis: hormone levels: ACTH, FSH, LH, prolactin, ADH, oxytocin, testosterone | Diagnostic evaluation Pituitary scan MRI of brain with pituitary Endocrinology consult | Grade 2: | Hold ICPI |
| Adrenal crisis   |      | Adrenalitis: fatigue, malaise, hypotension, vague gastrointestinal symptoms, weight loss, hypoglycemia | Hormone repletion (may require lifetime hormone replacement) | Grade 3–4: | Permanently discontinue ICPI |
| Hypophysitis:    |      | Hypophysitis: hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone | If am cortisol <3 µg/dL: adrenal insufficiency | Grade 1: | Continue ICPI |
| Adrenal insufficiency | Primary adrenal insufficiency: low cortisol, high ACTH | If am cortisol <3 µg/dL: adrenal insufficiency | Grade 2: | Hold ICPI |
| Adrenal crisis   |      | Secondary adrenal insufficiency: low cortisol, low ACTH | Endocrinology consult | Grade 3–4: | Permanently discontinue ICPI |
| Hypophysitis:    |      | Hypophysitis: hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone | If am cortisol <3 µg/dL: adrenal insufficiency | Grade 1: | Continue ICPI |
| Adrenal insufficiency | Laboratory: Adrenalitis: hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone | Laboratory: CBC and blood cultures to rule out sepsis | Grade 2: | Hold ICPI |
| Adrenal crisis   |      | Adrenalitis: hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone | Laboratory: CBC and blood cultures to rule out sepsis | Grade 3–4: | Permanently discontinue ICPI |
| Hypophysitis:    |      | Hypophysitis: hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone | Laboratory: CBC and blood cultures to rule out sepsis | Grade 1: | Continue ICPI |
| Adrenal insufficiency | Laboratory: Adrenalitis: hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone | Laboratory: CBC and blood cultures to rule out sepsis | Grade 2: | Hold ICPI |
| Adrenal crisis   |      | Adrenalitis: hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone | Laboratory: CBC and blood cultures to rule out sepsis | Grade 3–4: | Permanently discontinue ICPI |

*ICPI: Immune Checkpoint Inhibitor

### Hepatic

| Organ | ImAE | Symptoms | Evaluation | Grading* | Management |
|-------|------|----------|------------|----------|------------|
| Elevated AST/ALT | Nausea | Elevated AST/ALT | Laboratory: liver enzymes (AST, ALT, ALK, total and direct bilirubin) every 3 days, coagulation panel | Grade 1: | AST or ALT > ULN to 3 × ULN and/or total bilirubin > ULN to 1.5 × ULN |
| Elevated bilirubin | Decreased appetite | Elevated bilirubin | Diagnostic evaluation: Liver ultrasound | Grade 2: | AST or ALT > ULN to 3 × ULN and/or total bilirubin > ULN to 1.5 × ULN |
| Hepatitis | Fever | Elevated bilirubin | Gastroenterology consult | Grade 3–4: | AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN |
| | Vague abdominal discomfort | Elevated bilirubin | Hepatology consult | Grade 1: | AST or ALT > 3 × ULN and/or total bilirubin > 1.5 × ULN |
| | RUQ pain | Elevated bilirubin | Consider liver biopsy to confirm diagnosis | Grade 2: | AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN |
| | Dehydration | Elevated bilirubin | Consider liver biopsy to confirm diagnosis | Grade 3–4: | AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN |
| | Jaundice | Elevated bilirubin | Consider liver biopsy to confirm diagnosis | Grade 1: | AST or ALT > 3 × ULN and/or total bilirubin > 1.5 × ULN |
| | Bleeding, bruising | Elevated bilirubin | Consider liver biopsy to confirm diagnosis | Grade 2: | AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN |
| | Dark urine | Elevated bilirubin | Consider liver biopsy to confirm diagnosis | Grade 3–4: | AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN |

*ICPI: Immune Checkpoint Inhibitor

(Continued)
### Table 3 (Continued)

| Organ            | ImAE                  | Symptoms                          | Evaluation                                      | Grading | Management                                      |
|------------------|-----------------------|-----------------------------------|-------------------------------------------------|---------|------------------------------------------------|
| Pulmonary        | Ground glass opacities | Dry cough                         | Oxygen saturation at rest and with ambulation   | Grade 1 | Grade 1: Consider holding ICPI                 |
|                  | on imaging            | Wheezing                          | Laboratory: CBC                                 | Grade 2 | Oxygen support; albuterol nebulizer, PRN; steroid inhaler, PRN |
|                  | Pneumonitis           | Tachypnea/tachycardia             | Rule out:                                        | Grade 3 | Monitor every 2–3 days                         |
|                  | Sarcoid-like lung     | Shortness of breath at rest       | Infectious cause                                 | Grade 4 | Grade 2: Hold ICPI                            |
| disease          | disease               | Shortness of breath at exertion   | Lympangitic spread                               |         | MPS 1–2 mg/kg/day                              |
|                  |                      | Hypoxia                           | Pulmonary embolism                               |         | Daily monitoring                               |
|                  |                      | Increased oxygen requirements     | Pleural effusion                                 |         | If imAE resolves to baseline, consider resuming treatment after steroid tapered over 4–6 weeks |
|                  |                      | Chest pain                        | Consult                                          |         | Grade 3: Permanently discontinue ICPI          |
|                  |                      | Radiographic changes              | Interventional pulmonology                       |         | MPS 1–2 mg/kg/day increasing to 2–4 mg/kg/day if needed; taper as listed for Grade 2 |
|                  |                      |                                   | Infectious disease                               |         | Refractory:                                    |
|                  |                      |                                   | Diagnostics:                                     |         | Consider additional immunosuppressant (eg, infliximab) |
|                  |                      |                                   | CT scan                                          |         | Grade 1:                                      |
|                  |                      |                                   | Bronchoscopy with biopsy                         |         | Hold all nephrotoxic drugs                    |
|                  |                      |                                   | PFTs                                             |         | Hydration                                      |
|                  |                      |                                   |                                                   |         | Grade 2–3:                                     |
|                  |                      |                                   | Monitor serum creatinine                         |         | Hold ICPI                                     |
|                  |                      |                                   |                                                   |         | Hydration                                      |
|                  |                      |                                   |                                                   |         | Monitor serum creatinine every 2–3 days       |
|                  |                      |                                   |                                                   |         | MPS 0.5–1.0 mg/kg/day; if no improvement increase to 1–2 mg/kg/day |
|                  |                      |                                   |                                                   |         | Grade 4:                                      |
|                  |                      |                                   | Life-threatening                                  |         | Permanently discontinue ICPI                  |
|                  |                      |                                   |                                                   |         | MPS 1–2 mg/kg/day with taper as listed for Grade 2–3 |
| Renal            | Interstitial nephritis| Often asymptomatic                | Laboratory: serum creatinine, urinalysis         | Grade 1 | Grade 1:                                      |
|                  | Granulomatous         | Increase in serum creatinine      | Nephrology consult                               | Grade 2 | Hold all nephrotoxic drugs                    |
|                  | nephritis             | Vague nausea                      | Renal ultrasound                                 | Grade 3 | Hydration                                      |
|                  | Glomerular lupus-like | Emesis                            | Renal biopsy                                     | Grade 4 | Grade 2–3:                                     |
| nephropathy      | Renal insufficiency   | Decreased urine output            |                                                   |         | Hold ICPI                                     |
|                  | Renal failure         | Cloudy/dark urine                 |                                                   |         | Hydration                                      |
|                  |                      | Blood in urine                    |                                                   |         | Monitor laboratory results at least weekly    |
|                  |                      | Ankle swelling                    |                                                   |         | Grade 2–3:                                     |
|                  |                      |                                   |                                                   |         | Hold ICPI                                     |
|                  |                      |                                   |                                                   |         | MPS 0.5–1.0 mg/kg/day                          |
|                  |                      |                                   |                                                   |         | Grade 4:                                      |
|                  |                      |                                   |                                                  |         | Permanently discontinue ICPI                  |
|                  |                      |                                   |                                                   |         | MPS 1–2 mg/kg/day with taper as for Grade 2–3 |
| Pancreatic       | Elevated amylase and  | May be asymptomatic               | Laboratory: amylase and lipase levels, blood glucose | Grade 1 | Grade 1:                                      |
|                  | lipase                | RUQ abdominal pain                 | Pancreatic ultrasound                            | Grade 2 | Monitor laboratory results at least weekly     |
|                  | Pancreatitis          | Nausea                            | CT scan                                          | Grade 3 | Grade 2–3:                                     |
|                  | Type 1 diabetes       | Vomiting                          | Gastroenterology consult                         | Grade 4 | Hold ICPI                                     |
| mellitus         | mellitus              | Increase in stool frequency, bulk, or odor | Endoscopy                                        |         | MPS 0.5–1.0 mg/kg/day                          |
|                  |                      | Steatorrhea                       |                                                   |         | Grade 4:                                      |
|                  |                      |                                   |                                                   |         | Permanently discontinue ICPI                  |
|                  |                      |                                   |                                                   |         | MPS 1–2 mg/kg/day with taper as for Grade 2–3 |

(Continued)
### Table 3 (Continued)

| Organ          | ImAE                      | Symptoms                                | Evaluation               | Grading<sup>a</sup>                                                                 | Management                                                                 |
|----------------|---------------------------|-----------------------------------------|--------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| **Ocular**     | Uveitis                   | Painful, itchy, watery eyes             | Rule out infection       | Grade 1: Asymptomatic or mild symptoms                                                  | Grade 1: Continue ICPI                                                    |
|                | Episcleritis              | Decreased acuity                        | Ophthalmology consult    | Grade 2: Symptoms limiting ADL                                                         | Lubricating eye drops                                                   |
|                | Conjunctivitis            | Visual deficits                         |                          | Grade 2: Symptoms limiting ADL                                                         | Grade 2: Continue ICPI                                                   |
|                | Iritis                    | Dry eyes                                |                          | Grade 3: Anterior uveitis                                                              | Topical corticosteroid eye drops                                         |
|                | Blepharitis               | Inflammation                            |                          | Grade 3: Anterior uveitis                                                              | Consider holding ICPI                                                   |
|                | Orbital inflammation     | Erythematous soft tissue                |                          | Grade 3: Symptoms limiting self-care                                                    | Grade 3: Hold ICPI                                                      |
|                |                           | Injected conjunctiva                    |                          | Grade 4: Posterior or panuveitis                                                        | MPS 0.5–1.0 mg/kg/day                                                    |
|                |                           |                                         |                          | If imAE resolves to Grade 1, taper steroid dose over 4–6 weeks and consider resuming   | Grade 4: Permanently discontinue ICPI                                    |
|                |                           |                                         |                          | ICPI<sup>b</sup>                                                                       | MPS 1–2 mg/kg/day with taper as for Grade 3                               |
| **Musculoskeletal** | Muscular inflammation | Mild joint ache                         | Rheumatology consult     | Grade 1: Arthralgia; mild pain                                                         | Grade 1: Continue ICPI                                                    |
|                | Arthritis                 | Joint swelling                           | Orthopedic consult       | Grade 2: Arthritis; moderate pain; limiting instrumental ADL                           | Grade 2: Hold ICPI<sup>c</sup>                                           |
|                | Erythematous lupus        | Joint erythema                          |                          | Grade 2: Arthritis; moderate pain; limiting instrumental ADL                           | MPS 0.5–1.0 mg/kg/day                                                    |
|                | Polymyalgia rheumatic     | Decreased range of motion of joints     |                          | If AE resolves to Grade 1, taper steroid dose over 4–6 weeks and consider resuming ICPI<sup>b</sup> | Grade 3: Permanently discontinue ICPI                                    |
|                | Giant cell arteritis      |                                         |                          | MPS 1–2 mg/kg/day with taper as for Grade 2                                             | Grade 3: Permanently discontinue ICPI                                    |
|                | Arthralgia                |                                         |                          |                                                                                       | Grade 3: Permanently discontinue ICPI                                    |
|                | Myalgia                   |                                         |                          | Grade 3: Permanently discontinue ICPI                                                    | Grade 3: Permanently discontinue ICPI                                    |

*ICPI* indicates immune checkpoint inhibitor.
| Organ                  | ImAE            | Symptoms                               | Evaluation               | Grading*                  | Management                                      |
|-----------------------|-----------------|----------------------------------------|--------------------------|---------------------------|------------------------------------------------|
| Neurologic            | Neuralgia       | Unusual weakness                      | MRI of brain             | Grade 1:                  | Continue ICPI                                   |
|                       | Guillain–Barre  | Numbness                               | Rule out: CVA, infection, brain metastasis, leptomeningeal disease | Asymptomatic or mild symptoms |
|                       | syndrome        | Difficulty walking                     | Neurology consult        | Grade 2:                  | Safety measures                                 |
|                       | Aseptic or lymphocytic meningitis | Difficulty performing daily tasks (writing, dressing, feeding) | Lumbar puncture to evaluate CSF | New-onset moderate symptoms limiting instrumental ADLs |
|                       | Posterior reversible encephalopathy | Neck stiffness                     |                          | Grade 3–4:                | Relapse of care.                  |
|                       | Enteric neuropathy | Headache                               |                          | New-onset severe symptoms limiting self-care | |
|                       | Transverse myelitis | Confusion                             |                          | Life-threatening consequences | |
|                       |                 | Sleepiness                             |                          |                           |                                                |
|                       |                 | Memory difficulties                    |                          |                           |                                                |
|                       |                 | Hallucinations                         |                          |                           |                                                |
|                       |                 | Seizures                               |                          |                           |                                                |
| Cardiac               | Pericarditis    | Chest pain                             | Laboratory: troponin, BNP | Grade 1:                  | Continue ICPI                                   |
|                       | Myocarditis     | Dyspnea                                | ECG                      | Asymptomatic              | Safety measures                                 |
|                       | Pericardial effusion | Fluid retention                   | Echocardiogram           | Subtle ECG or physical findings (eg, rub) | Rehabilitation                                |
|                       |                 | Lower extremity edema                  | CT of chest              | Grade 2:                  | Grade 2: Hold ICPI<sup>e</sup>                |
|                       |                 | Rapid/abnormal heart rhythms           | MRI of heart             | Symptomatic pericarditis (eg, chest pain) | MPS 0.5–1.0 mg/kg/day                         |
|                       |                 | Fatigue                                | Cardiology consult       | Grade 3:                  | If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks<sup>f</sup> |
|                       |                 | Muscle pain                            |                          | Symptomatic pericarditis with physiologic consequences | |
|                       |                 |                                        |                          | Grade 4:                  | Refractory: If worsens, consider additional immunosuppressant therapy |
|                       |                 |                                        |                          | Life-threatening consequences | |

<sup>a</sup> If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks.

<sup>b</sup> If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks.<sup>c</sup>

<sup>c</sup> For Grade 2, taper prednisone equivalent 1–2 mg/kg/day and yes taper for Grade 3–4.

<sup>d</sup> For Grade 2, taper prednisone equivalent 1–2 mg/kg/day and yes taper for Grade 3–4.

<sup>e</sup> If imAE resolves to Grade 1, taper prednisone equivalent 1–2 mg/kg/day and yes taper for Grade 3–4.

<sup>f</sup> Medical intervention as indicated.

<sup>g</sup> Refractory: If worsens, consider additional immunosuppressant therapy.

<sup>h</sup> Medical intervention as necessary.

<sup>i</sup> Permanent discontinuation of ICPI.

<sup>j</sup> Permanent discontinuation of ICPI.

<sup>k</sup> Permanent discontinuation of ICPI.

<sup>l</sup> Permanent discontinuation of ICPI.

<sup>m</sup> Permanent discontinuation of ICPI.
### Table 3 (Continued)

| Organ                  | ImAE                     | Symptoms    | Evaluation     | Grading[^b] | Management                      |
|------------------------|--------------------------|-------------|----------------|-------------|----------------------------------|
| Hematologic            | Cytopenia                | Fatigue     | Monitor CBC    | Grade 1:    | Grade 1–2: Continue ICPI         |
|                        |                          | Weakness    | Rule out infection | ANC < LLN–1 500/mm[^3] | Close monitoring |
|                        |                          | Dyspnea     | Rule out DIC   | Grade 2:    | Grade 3: Hold ICPI[^d]           |
|                        |                          | Petechiae   | Hematology consult | Hgb < LLN–1.0 g/dL | Monitor closely |
|                        |                          |             |                | Grade 3:    | If no improvement, consider initiation of steroid with taper over 4–6 weeks once imAE resolves to Grade 1[^b] |
|                        | Acquired hemophilia A    | Bruising    |                | ANC < 1500–1000/mm[^3] | Grade 4: Permanently discontinue ICPI |
|                        |                          | Bleeding    |                | Hgb < 10.0–8.0 g/dL | Initiation of steroids with taper as for Grade 3 |
|                        |                          |             |                | Plt < 75,000–50,000/mm[^3] |                                    |
|                        |                          |             |                | ANC < 1500–5000/mm[^3] |                                    |
|                        |                          |             |                | Hgb < 8.0 g/dL |                                    |
|                        |                          |             |                | Plt < 50,000–25,000/mm[^3] |                                    |
|                        |                          |             |                | ANC < 25,000/mm[^3] |                                    |
|                        |                          |             |                | Hgb: life-threatening consequences; urgent intervention indicated |                                    |
|                        |                          |             |                | Plt < 25,000/mm[^3] |                                    |

**Notes:**
- Based on published management algorithms[^2-7,88-97] and authors’ clinical experience.
- Grading based on NCI Common Terminology Criteria for Adverse Events v4.0.
- For Yervoy (ipilimumab): hold ICPI if Grade 2 rash, consider oral systemic steroid (0.5–1.0 mg/kg/day) if persists >1 week or interferes with ADL. For Imfinzi (durvalumab): hold ICPI if Grade 2 for >1 week. For Yervoy (ipilimumab): permanently discontinue if Grade 2 imAE persists 26 weeks or unable to reduce prednisone to ≤7.5 mg prednisone or equivalent per day or to complete four-dose course within 16 weeks. For Yervoy (ipilimumab): resume treatment when imAE resolves to Grade 1 or less and is controlled with ≤7.5 mg/kg prednisone or equivalent per day. For Keytruda (pembrolizumab): permanently discontinue if any Grade 3 imAE recurs or if any persistent Grade 2 or 3 imAE (excluding endocrinopathies) does not resolve to Grade 1 within 12 weeks with ≤10 mg prednisone or equivalent per day. For Yervoy (ipilimumab): resume treatment when imAE resolves to Grade ≤1 and corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day. For Yervoy (ipilimumab): initiate 0.5 mg/kg/day prednisone or equivalent if symptoms persist >1 week, worsen, or recur. For Yervoy (ipilimumab) or combination Yervoy + Opdivo (ipilimumab + nivolumab): permanently discontinue. For Yervoy (ipilimumab): permanently discontinue Imfinzi (durvalumab) for Grade 3 gastrointestinal imAE. For Imfinzi (durvalumab): permanently discontinue Bavencio (avelumab) if Grade 3 imAE is recurrent. For Yervoy (ipilimumab): temporarily discontinue if ≥1 week, worsen, or recur. For Yervoy (ipilimumab) or combination Yervoy + Opdivo (ipilimumab + nivolumab): permanently discontinue. For Yervoy (ipilimumab) or combination Yervoy + Opdivo (ipilimumab + nivolumab): permanently discontinue. Begin taper if AE improves to Grade 2 for Opdivo (nivolumab) or if liver function tests improve for Yervoy (ipilimumab). For Keytruda (pembrolizumab): permanently discontinue if Grade 3 with ≥8 × ULN AST/ALT or ≥5 × ULN total bilirubin or if Grade 4. Hold if Grade 3 with ≥8 × ULN AST/ALT or ≤5 × ULN total bilirubin. Permanently discontinue Yervoy (ipilimumab), Keytruda (pembrolizumab), or Imfinzi (durvalumab) for Grade 3 nephritis. Permanently discontinue Yervoy (ipilimumab) for Grade 3 pancreatitis. Discontinue Keytruda (pembrolizumab) or Opdivo (nivolumab) if recurrent Grade 2 or 3. For grade 4 serum amylase or lipase elevation, hold Yervoy (ipilimumab) and consider resuming treatment once imAE resolves to Grade ≤1 within 12 weeks and corticosteroids reduced to ≤10 mg/day oral prednisone. Hold Imfinzi (durvalumab) for Grade 2–4 type 1 diabetes mellitus; resume treatment if type 1 diabetes mellitus resolves to Grade ≤1. Permanently discontinue Yervoy (ipilimumab) if Grade ≥2 or Grade 1 not responding to steroids within 2 weeks or requiring systemic therapy. Permanently discontinue Opdivo (nivolumab), Keytruda (pembrolizumab), Tecentriq (atezolizumab), or Bavencio (avelumab) if Grade 3. For Tecentriq (atezolizumab): permanently discontinue for any grade menigitis or encephalitis and treat with steroids (MPS, 1–2 mg/kg/day); use medical intervention as appropriate for myasthenia syndrome/myasthenia gravis or Guillain-Barre syndrome. For Yervoy (ipilimumab) and Opdivo (nivolumab): treat symptoms as per institutional guidelines. For Yervoy, begin tapering steroids when Grade 3–4 imAE resolves to Grade 2. For Opdivo (nivolumab), resume ICPI if Grade 2 imAE resolves to baseline.

**Abbreviations:** ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; ADL, activities of daily living; AE, adverse event; ALK, alkaline phosphatase; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; BNP, brain natriuretic peptide; CBC, complete blood count; CMP, comprehensive metabolic panel; C&S, culture and sensitivity; CSF, cerebrospinal fluid; CT, computerized tomography; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; FSH, follicle-stimulating hormone; GI, gastrointestinal; Hgb, hemoglobin; ICPI, immune checkpoint inhibitor; imAE, immune-mediated adverse event; IV, intravenous; LH, luteinizing hormone; LLN, lower limit of normal; MPS, methylprednisolone; MRI, magnetic resonance imaging; NCI, National Cancer Institute; FTTs, pulmonary function tests; Pt, platelets; PRN, as needed; r/o, rule out; RUQ, right upper quadrant; TSH, thyroid-stimulating hormone; ULN, upper limit of normal; WBC, white blood cell count.
Figure 1  Time to onset of immune-mediated toxicities (median and range).^{22–27}

Notes: Onset patterns of imAEs in patients receiving ICPI treatment by organ system and target pathway: CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (atezolizumab, avelumab, and durvalumab).

- Dermatitis in ipilimumab studies; immune-mediated rash in nivolumab and nivolumab + ipilimumab studies.
- Enterocolitis in ipilimumab studies; colitis in nivolumab, pembrolizumab, avelumab, and nivolumab + ipilimumab studies; colitis or diarrhea in atezolizumab and durvalumab studies.
- Hypopituitarism, adrenal insufficiency, hypothyroidism, hyperthyroidism, hypogonadism, thyroiditis, Cushing’s syndrome, and Graves’ ophthalmopathy.
- Hypothyroidism and hyperthyroidism are combined for avelumab.
- Hepatitis.
- Pneumonitis.
- Nephritis or renal dysfunction in nivolumab and nivolumab + ipilimumab studies; nephritis in pembrolizumab studies.
- Neuropathy in ipilimumab studies and encephalitis in nivolumab and nivolumab + ipilimumab studies.

Abbreviations: d, days; GI, gastrointestinal; ICPI, immune checkpoint inhibitor; imAEs, immune-mediated adverse events; m, months; T1DM, type 1 diabetes mellitus.

| Organ System | n | Time to Onset (Median and Range) |
|--------------|---|---------------------------------|
| Dermatologic | n = 76 | 22 d (11–14 d) | 2.4 m (1.1 m) | 16.6 m (2.1–2.2 m) | 25.8 m (3.5 m) |
| GI | n = 62 | 1.4–1.7 m (1.1 m) | 3.4 m (2.5 m) | 4.8–5.4 m (3.3 m) | |
| Endocrine | | 21 d–1.7 m (3.5 m) | 4.9 m (2.7 m) | 2.1 m (2.5 m) | |
| All | n = 132 | 2.1–2.2 m (14 d) | 2.6 m (2.5 m) | 4.8–5.4 m (3.5 m) | 21.9 m (14.2 m) |
| Hypophysitis | n = 12 | 2.7 m (1.5 m) | 3.0 m (2.0 m) | |
| Adrenal insufficiency | n = 20 | 2.6 m (2.5 m) | 4.4 m (3.4 m) | 21.0 m (14.2 m) |
| Hypothyroidism | n = 237 | 2.7 m (2.4 m) | 4.4 m (3.1 m) | 18.9 m (13.0 m) |
| Hyperthyroidism | n = 54 | 23 d (14 d) | 3.2–4.9 m (2.8 m) | 31.0 m (13.0 m) |
| Hepatic | n = 73 | 1.4–2.0 m (1.5 m) | 3.3 m (2.1 m) | 21.4 m (15.0 m) |
| Pulmonary | n = 61 | 2.1 m (2.0 m) | 3.3 m (3.2 m) | 22.3 m (19.3 m) |
| Renal | n = 23 | 1.7 m (1.6 m) | 3.0 m (2.9–3.3 m) | 18.7 m (13.9 m) |
| Pancreatic (T1DM) | n = 17 | 2.7 m (1.7 m) | 4.4 m (5.1 m) | 22.0 m (12.8 m) |
| Neurologic | n = 9 | 1.7 m (1.6 m) | 7.2 m (6.4 m) | 27.4 m (10.5 m) |

| Anti-CTLA-4 | Anti-PD-1 | Anti-CTLA-4 + Anti-PD-1 | Anti-PD-L1 |
|-------------|-----------|--------------------------|-----------|
| Ipilimumab 3 mg/kg | Nivolumab | Nivolumab + Ipilimumab | Atezolizumab |
| Ipilimumab 10 mg/kg | Pembrolizumab | | Durvalumab |
| Nivolumab | | | Avelumab |

Figure 1: Time to onset of immune-mediated toxicities (median and range).^{22–27}

Notes: Onset patterns of imAEs in patients receiving ICPI treatment by organ system and target pathway: CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (atezolizumab, avelumab, and durvalumab). Dermatitis in ipilimumab studies; immune-mediated rash in nivolumab and nivolumab + ipilimumab studies. Enterocolitis in ipilimumab studies; colitis in nivolumab, pembrolizumab, avelumab, and nivolumab + ipilimumab studies; colitis or diarrhea in atezolizumab and durvalumab studies. Includes hypopituitarism, adrenal insufficiency, hypothyroidism, hyperthyroidism, hypogonadism, thyroiditis, Cushing’s syndrome, and Graves’ ophthalmopathy. Hypothyroidism and hyperthyroidism are combined for avelumab. Hepatitis. Pneumonitis. Nephritis or renal dysfunction in nivolumab and nivolumab + ipilimumab studies; nephritis in pembrolizumab studies. Neuropathy in ipilimumab studies and encephalitis in nivolumab and nivolumab + ipilimumab studies.

Abbreviations: d, days; GI, gastrointestinal; ICPI, immune checkpoint inhibitor; imAEs, immune-mediated adverse events; m, months; T1DM, type 1 diabetes mellitus.
Combination anti-CTLA-4 and anti-PD-1 therapy with ipilimumab and nivolumab.\textsuperscript{4,9} Colitis has been observed in 7–16\% of patients receiving anti-CTLA-4 therapy (ipilimumab: 3 mg/kg, 7–12\%;\textsuperscript{4,9,39,42} 10 mg/kg, 16\%\textsuperscript{46}), 1–3\% of patients treated with anti-IPD-1/IPD-L1 antibodies (1\% for nivolumab,\textsuperscript{4,6,11,41,62} atezolizumab,\textsuperscript{7,13,17,44} and durvalumab;\textsuperscript{30} avelumab, 2\%;\textsuperscript{26} pembrolizumab, 1–3\%\textsuperscript{2,16,18,20,42,43}), and 12–18\% of patients treated with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{4,9} Rates of Grade 3/4 diarrhea or colitis are low (≤4\%) in patients receiving anti-PD-1 or anti-PD-L1 monotherapy,\textsuperscript{2,4,6,7,10,11,13,15–17,20,41–44,50,51,59,60,62} but tend to be higher in patients treated with anti-CTLA-4 monotherapy (ipilimumab, 2–11\%\textsuperscript{4,9,39,40,42} or combination anti-CTLA-4 and anti-PD-1 therapy with nivolumab and ipilimumab (8–13\%).\textsuperscript{4,9} The median onset of immune-mediated diarrhea and/or colitis ranges from 21 days to 5.3 months in patients treated with ICPIs in clinical registration studies (Figure 1).\textsuperscript{22–27} Deaths from intestinal perforation from colitis have been reported at very low rates (<1\%) in anti-CTLA-4 monotherapy studies at both 3 mg/kg and 10 mg/kg doses.\textsuperscript{22,40}

Endocrine
Autoimmune endocrinopathies (predominantly Grade 1 or 2) have been reported in patients treated with ICPIs in clinical studies, including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis (pituitary inflammation), and adrenal insufficiency.\textsuperscript{22–27} Rates of all-grade endocrinopathies are generally low in patients receiving anti-PD-1/IPD-L1 therapy, with <10\% of patients experiencing each individual endocrinopathy.\textsuperscript{22–27} Higher rates are reported in patients treated with anti-CTLA-4 therapy either as monotherapy (ipilimumab 3 mg/kg, 8–15\%;\textsuperscript{4,9,39} ipilimumab 10 mg/kg, 38\%\textsuperscript{46}) or in combination with anti-PD-1 therapy (ipilimumab + nivolumab, 30–31\%\textsuperscript{4,9}). Rates of Grade 3/4 endocrinopathies are generally low in patients receiving ICPI monotherapy (anti-CTLA-4: ipilimumab 3 mg/kg, 1.8\%;\textsuperscript{22} anti-PD-1/IPD-L1: nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab, <1\%\textsuperscript{2,4,24–27} for each individual endocrinopathy); however, higher rates have been reported with high-dose anti-CTLA-4 (ipilimumab 10 mg/kg, 8\%\textsuperscript{22} and combination anti-CTLA-4 and anti-PD-1 (ipilimumab + nivolumab, 5\%).\textsuperscript{4,9} Most cases of immune-mediated hypothyroidism can be adequately treated with hormone replacement, and ICPI therapy can be continued.

Hypophysitis and thyroid dysfunction are the most common endocrine imAEs associated with ICPI treatment. Hypophysitis (median onset 2–5 months;\textsuperscript{23,24,57} Figure 1) rarely occurred in patients treated with anti-PD-1 or anti-PD-L1 monotherapy in clinical studies (<1% for nivolumab, pembrolizumab, atezolizumab, or durvalumab),\textsuperscript{23–25,27} but has been observed in 2–7% of patients receiving anti-CTLA-4 therapy (ipilimumab) at the 3 mg/kg dose\textsuperscript{4,9,42} and 18\% of patients receiving the 10 mg/kg dose,\textsuperscript{40} and in 8–13\% of patients treated with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{4,9} The vast majority of patients who experience Grade ≥2 hypophysitis fail to recover pituitary function and require lifelong hormone replacement therapy.\textsuperscript{22,57,68} Adrenal insufficiency can arise secondary to hypopituitarism (≤1\%, anti-PD-1 monotherapy [nivolumab]\textsuperscript{23} or anti-PD-L1 monotherapy [atezolizumab,\textsuperscript{25} avelumab,\textsuperscript{26} durvalumab]\textsuperscript{27}); 5\%, combination anti-CTLA-4 and anti-PD-1 [ipilimumab + nivolumab]\textsuperscript{23}), typically manifesting as dehydration, hypotension, hyponatremia, and/or hyperkalemia similar to sepsis syndrome.\textsuperscript{69}

Hypothyroidism has been reported in 9\% of patients treated with anti-PD-1 (nivolumab or pembrolizumab)\textsuperscript{23,24} or high-dose anti-CTLA-4 monotherapy (ipilimumab 10 mg/kg),\textsuperscript{40} in 2–13\% of patients receiving standard-dose anti-CTLA-4 monotherapy (ipilimumab 3 mg/kg),\textsuperscript{4,9,39,42} in 4–5\% of patients treated with anti-PD-L1 antibodies (atezolizumab, 4%;\textsuperscript{25} avelumab, 5%;\textsuperscript{26} durvalumab, 6%\textsuperscript{27}), and in 15–17\% of patients receiving combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{4,9} In clinical registration studies, the median onset of hypothyroidism ranged from 1 to 5 months,\textsuperscript{23–27} sometimes following a brief period of hyperthyroidism (Figure 1). Hypothyroidism does not resolve for most patients, resulting in the potential need for long-term hormone supplementation.\textsuperscript{23–27,47,70} Hyperthyroidism, which is less common than hypothyroidism, resolves in the vast majority of patients.\textsuperscript{71}

Hepatic
Hepatotoxicity, including hepatitis and elevated alanine transaminase (ALT)/aspartate transaminase (AST), has been documented in patients treated with ICPIs.\textsuperscript{57,58} In patients treated with anti-CTLA-4 therapy, the rate of hepatic adverse events ranged from 4\% to 9\% (ipilimumab 3 mg/kg)\textsuperscript{4,9,39} to 25\% (ipilimumab 10 mg/kg),\textsuperscript{40} with Grade 3/4 events occurring in 0\% to 2\% to 11\%, respectively. Hepatotoxicity occurred in 2–6\% (0–3\% Grade 3/4) of the patients treated with anti-PD-1 monotherapy (nivolumab)\textsuperscript{6,11,15,41,62} and in 30–32\% (13–19\% Grade 3/4) of the patients receiving combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{4,9} Immune-mediated hepatitis, reported in ≤2\% of patients treated with ICPI monotherapy\textsuperscript{23–27,39} (excluding ipilimumab 10 mg/kg dose, 15\%),\textsuperscript{22} typically presents...
at 1–3 months and resolves with steroid treatment in most patients (Figure 1).\textsuperscript{22–27} Although rare, fatal cases of immune-mediated hepatitis have occurred with ICPI monotherapy (0.2%, ipilimumab 3 mg/kg;\textsuperscript{22} 0.1%, nivolumab;\textsuperscript{26} 0.5%, durvalumab\textsuperscript{27}). Elevated ALT/AST with concomitant elevated bilirubin may indicate a more serious hepatic injury.\textsuperscript{72,73}

**Pulmonary**

Immune-mediated pneumonitis is a rare but potentially serious adverse event, occurring in <1% of patients treated with anti-CTLA-4 antibodies (ipilimumab 3 mg/kg or 10 mg/kg doses),\textsuperscript{22} in 1–3% of those receiving anti-PD-1/PD-L1 (nivolumab, pembrolizumab, or atezolizumab, 3%;\textsuperscript{23–25} avelumab, 1%;\textsuperscript{26} durvalumab, 0.5%),\textsuperscript{25} and in 6% of those receiving combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{23} Immune-mediated pneumonitis has been reported more frequently in patients receiving anti-PD-1 therapy (nivolumab or pembrolizumab) for NSCLC (3–6%)\textsuperscript{11,16,43,50} than for melanoma (1–2%; Table 2).\textsuperscript{2,4,41,42,62,66} Pneumonitis has a median onset ranging from 2 months to 4 months (Figure 1).\textsuperscript{23–27}

**Rare adverse events**

A wide array of additional imAEs has been observed at low rates (<2%) in patients receiving ICPI monotherapy across other organ systems, including renal, pancreatic, ocular, musculoskeletal, neurological, cardiovascular, and hematologic toxicities (Table 3).\textsuperscript{22–27} In general, rates of these imAEs are similar or slightly higher in patients receiving combination anti-CTLA-4 and anti-PD-1 antibodies.\textsuperscript{23}

**Renal**

Immune-mediated nephritis has been observed at low rates in patients receiving anti-CTLA-4 therapy (ipilimumab, <1%),\textsuperscript{22} anti-PD-1 antibodies (nivolumab, 1.2%;\textsuperscript{23} pembrolizumab, <0.3%\textsuperscript{34}), anti-PD-L1 antibodies (avelumab, 0.1%;\textsuperscript{26} durvalumab, ≤1%),\textsuperscript{27} and combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab; 2.2%).\textsuperscript{23} The onset of renal imAEs typically occurs earlier with anti-CTLA-4 therapy (2–3 months) than with anti-PD-1 antibodies (3–10 months).\textsuperscript{74}

**Pancreatic**

Pancreatic toxicities reported in clinical studies with ICPIs include elevated amylase/lipase, pancreatitis, and type 1 diabetes mellitus. Pancreatitis was observed in ≤1% of patients receiving ICPI monotherapy\textsuperscript{22–26} (excluding anti-CTLA-4 therapy with ipilimumab 10 mg/kg, 1.3%)\textsuperscript{22} or combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{23} Type 1 diabetes mellitus has occurred at low rates in clinical trials of patients receiving anti-PD-1 antibodies (nivolumab, 0.9%; pembrolizumab, 0.2%)\textsuperscript{23,24} and anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab, ≤0.3%),\textsuperscript{25–27} and in 1.5% of patients treated with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{23} Although diabetes mellitus was not observed in clinical trials of anti-CTLA-4 monotherapy (ipilimumab),\textsuperscript{22} a report has described a case of diabetes insipidus associated with anti-CTLA-4 monotherapy (ipilimumab).\textsuperscript{75}

**Ocular**

Ocular imAEs have been reported at very low rates in clinical studies of ICPI monotherapy\textsuperscript{22–27} or combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{23} Ocular imAEs included uveitis, keratitis, iritis, scleritis, episceritis, and conjunctivitis, occurring in ≤1% of patients.\textsuperscript{22–27}

**Musculoskeletal**

Musculoskeletal imAEs have been reported at low rates in ICPI clinical studies, including polymyalgia rheumatica (<1%), myasthenia gravis, myositis (<1%), and arthritis (<2%).\textsuperscript{22–24,26,27} Although inflammatory arthritis has been reported with ICPI treatment in case series,\textsuperscript{76,77} the rate of this adverse event remains unclear due to inconsistent reporting of inflammatory arthritis in ICPI clinical studies.\textsuperscript{78}

**Neurologic**

A wide array of neurologic imAEs has been associated with ICPI treatment, including Guillain–Barre syndrome, myasthenia gravis, encephalitis, motor dysfunction, meningitis, demyelination, neuropahty, and nerve paresis. In clinical trials, these neurologic imAEs occurred in ≤1% of patients.\textsuperscript{22–27} A recent case series, however, noted a 14% incidence of neurologic toxicities in patients treated with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).\textsuperscript{79}

**Cardiovascular**

Cardiovascular imAEs occurred in ≤1% of patients treated with ICPIs in clinical studies, including myocarditis, pericarditis, vasculitis, and heart failure.\textsuperscript{22–24,26,27} Case reports and case series have also documented pericardial effusion, cardiomyopathy, and myocardial fibrosis and suggest that patients with preexisting cardiac pathology may be more susceptible to cardiovascular imAEs with ICPI therapy.\textsuperscript{80,81}

**Hematologic**

Hematologic imAEs, including hemolytic anemia and thrombocytopenic purpura, occurred in ≤1% of patients treated...
with ICPIs in clinical studies.22,24,26,27 Case reports have found hematologic imAEs in patients receiving anti-CTLA-4 or anti-PD-1 monotherapy, as well as combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).82–83

**Monitoring and evaluations of patients receiving ICPIs**

Prior to initiating treatment and periodically thereafter, the following laboratory parameters should be assessed: complete blood count, comprehensive metabolic panel (including kidney, liver, pancreatic, and thyroid function tests), and baseline oxygen saturation (including a “walking oxygen saturation” test to facilitate detection of a decrease in oxygen saturation levels that might warrant further diagnostic imaging).22–27,86 Assessment and documentation of baseline symptoms (Table 3) will allow providers to identify even subtle changes in the patient’s status that might represent an early manifestation of an imAE. In addition, oncology nurses could engage in follow-up telephone calls with patients taking ICPIs.87 If specific organ toxicity is suspected, careful evaluation strategies, subspecialty consults, and specialized testing (eg, imaging, bronchoscopy, and colonoscopy) may help rule out other possible causes of dysfunction and delineate the extent of the toxicity to determine optimal management strategies. The National Cancer Institute Common Terminology Criteria for Adverse Events v4.088 should be used to grade baseline symptoms as well as any new symptoms because evaluation and management change according to this grading. Detailed information on evaluation strategies is provided in Table 3.

Understanding the typical time of onset for the various imAEs can be helpful, but it is important to note that the range can be quite broad (Figure 1). Due to the variable onset of imAEs, it is critical to conduct ongoing assessment of symptoms during and after treatment. Patient assessment forms can be built into the electronic medical record (EMR) to capture and communicate potential imAEs.

**Special considerations for patients with preexisting autoimmune disease**

Although patients with preexisting autoimmune conditions were largely excluded from clinical trials, recent retrospective studies suggest that, with close monitoring, ICPIs can be safely and effectively used in this population.89,90 Of the 52 patients with preexisting autoimmune disease included in a recent retrospective study, the objective response rate with anti-PD-1 (nivolumab or pembrolizumab) therapy was 33%, with 38% of patients experiencing a flare of their underlying autoimmune condition at a median of 38 days from the first dose of ICPI.90 The flares were generally mild, with only two patients permanently discontinuing ICPI treatment due to the flare of their autoimmune disorder.90 Four patients permanently discontinued ICPI therapy due to the emergence of imAEs.90 Due to the potentially higher risk of side effects and exacerbation of the underlying condition in patients with a history of an autoimmune disease, significant caution should be exercised when considering these patients for treatment with ICPIs. Dosing should occur only after a frank discussion between the health care provider and the patient about the nature of the potential risks and benefits of such therapy.

**Management of immune-mediated toxicities**

For the current FDA-approved ICPIs, clinicians should follow published guidelines for the management of imAEs.57,58,91–97 These imAE algorithms vary based on the type and grade of toxicity, with some Grade 3 imAEs managed by holding therapy and others by permanent discontinuation of ICPI (Table 3). Depending on the organ system involved and the specific ICPI, some mild-to-moderate imAEs can be managed symptomatically, with the patient remaining on ICPIs, while others require the ICPI dose be held and treatment with corticosteroids until the imAE resolves to Grade 1 (Table 3). In patients with more severe (Grade 3/4 or prolonged Grade 2) imAEs, ICPIs are typically discontinued while imAEs are managed with corticosteroids or, if needed, other immunosuppressant agents such as infliximab or mycophenolate (Table 3).57,58,91–97 The occurrence of an imAE, regardless of the need for immunosuppressant therapy, does not appear to impact the efficacy of ICPI treatment.65,98 Because ICPI treatment is relatively new, physicians and nurses may find printed materials from product companies,22–27,99 publications outlining imAE management,57,58,92,97 and online algorithm tools96,93–96,100 helpful in determining optimal imAE management strategies for their patients (Table 4). Daily communication with the patient (in person or by phone) can help track the status of an imAE and may reduce the risk of mild imAEs escalating to more serious events.87

Patients receiving corticosteroid treatment for an imAE should be closely monitored. For mild imAEs, low doses of steroids are normally utilized (methylprednisolone [MPS] 0.5–1.0 mg/kg/day intravenously or oral prednisone equivalent), while more severe imAEs require higher steroid doses (MPS 1–4 mg/kg/day intravenously or oral prednisone equivalent).57,58,91–97 Patients with severe imAEs may require hospitalization, particularly if they are hemodynamically unstable.
In patients with serious imAEs, MPS is typically administered intravenously until the toxicity is stable, after which the patient can be transitioned to oral prednisone.57,58,91–97 Once the imAE has resolved to Grade 1 per clinical assessment, steroids should be tapered slowly over approximately 1 month or longer, as tapering steroids too quickly may result in a flare of the imAE. Patients should be monitored weekly during and immediately following the steroid tapering. Often ICPIs can be resumed once the imAE has resolved or stabilized to Grade 1.57,58,91–97 In some cases, patients may need to remain on physiologic doses of prednisone (≤10 mg) to stabilize imAEs at Grade 1.57,58,91–97 In some cases, patients may need to remain on physiologic doses of prednisone (≤10 mg) to stabilize imAEs at Grade 1.57,58,91–97

**Table 4 ICPI imAE management resources**

| Resource | URL |
|----------|-----|
| Print/online |  |
| Immune-mediated adverse reactions management guide for Yervoy94 | www.hcp.yervoy.com/servlet/servlet.FileDownload?file=00Pi000000TUzayEAD |
| Immune-mediated adverse reactions management guide for Opdivo monotherapy and Opdivo + Yervoy95 | www.opdivohcp.com/servlet/servlet.FileDownload?file=00Pi000000kLoKcEAK |
| Opdivo safety tool96 | www.opdivosafetytool.com/#/signs-symptoms-management-imars |
| A guide to monitoring patients during treatment with Keytruda97 | www.keytruda.com/static/pdf/adverse-reaction-management-tool.pdf |
| A nurse’s guide to Keytruda97 | www.keytruda.com/static/pdf/nurse-guide-to-treatment-monitoring.pdf |
| Tecentriq adverse event management brochure96 | www.tecentriq.com/content/dam/gene/tecentriq/Tecentriq-Adverse-Event-Management-Brochure.pdf |
| The clinicians’ guide to managing immune-related adverse events: an interactive algorithm tool96 | www.clinicaloptions.com/immuneeatool |
| Yervoy Risk Evaluation Mitigation Survey91 | www.fda.gov/downloads/drugs/drugsafety/ postmarketdrugsafetyinformationforpatientsandproviders/ucm249435.pdf |
| Imfinzi Immune-Mediated Adverse Events Management Handbook97 | www.imfinzi.com/content/dam/website-services/us/423-duvra0-com/resources/imAE_management_handbook.pdf |
| Lighthouse106 | www.lighthouseprogram.com |
| Published literature |  |
| Ipilimumab and its toxicities: a multidisciplinary approach97 | www.ncbi.nlm.nih.gov/pubmed/23774827 |
| Management of immune-related adverse events and kinetics of response with ipilimumab97 | www.ncbi.nlm.nih.gov/pubmed/22614989 |
| Management of adverse events following treatment with anti-programmed death-1 agents58 | www.ncbi.nlm.nih.gov/pubmed/27401894 |
| Prescribing information |  |
| Yervoy (prescribing information)22 | https://packageinserts.bms.com/pi/pi_yervoy.pdf |
| Opdivo (prescribing information)23 | https://packageinserts.bms.com/pi/pi_opdivo.pdf |
| Keytruda (prescribing information)24 | www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf |
| Tecentriq (prescribing information)25 | www.gene.com/download/pdf/tecentriq_prescribing.pdf |
| Bavencio (prescribing information)26 | www.bavencio.com/en_US/document/Prescribing-Information.pdf |
| Imfinzi (prescribing information)27 | www.azpicentral.com/imfinzi/imfinzi.pdf |

**Abbreviations:** ICPI, immune checkpoint inhibitor; imAE, immune-mediated adverse event.

**Education of patients, caregivers, and healthcare providers on the signs and symptoms of immune-mediated toxicities**

Most moderate and severe immune-mediated toxicities, if detected and treated early, can be managed effectively with oral or intravenous steroids; in rare steroid-refractory cases, other immunomodulatory agents (eg, infliximab or...
m cyclophosphamide or bendamustine, or rituximab in patients with bone marrow suppression. The decision to start systemic treatment depends on whether the patient is symptomatic and the severity of the symptoms. 

Patient and caregiver education

A sound patient management approach includes comprehensive education of patients and caregivers about how to recognize and report suspected symptoms of immune-mediated toxicities. Nurses are frequently the first and primary contact for patients throughout treatment. They can prepare patients with the knowledge to identify the signs and symptoms of imAEs and can highlight the importance of reporting symptoms immediately. Incorporating a multimodal approach to education, including printed materials, online education modules, or educational group sessions, can support patient education and understanding. Where available, patients may benefit from live group education or videos. Toxicity checklists (available from product companies) may assist patients in recognizing imAE symptoms. Companies’ websites offer online educational resources specifically designed for patients and caregivers. Most importantly, patients should be instructed to call their doctor’s office if they experience any new, worsening, or otherwise concerning symptoms (even when mild) to maximize early recognition of imAEs.

Education of other health care providers

As the use of ICPIs becomes ubiquitous across multiple different cancer diagnoses, it is imperative that all health care providers are informed regarding the potential for imAEs in patients being treated with these agents. Several modalities are available to assist other health care providers identify imAEs in this unique group of patients. Patient immunotherapy drug “wallet safety cards” can be a useful tool to alert other providers to be aware of potential imAEs associated with ICPIs, particularly during urgent visits. Health care professionals can...
call the phone number provided on the patient wallet safety card and benefit from peer discussion with the oncology team regarding symptoms, evaluation, and appropriate management. All staff members involved in the telephone triage process who might receive incoming patient phone calls must be educated in the use of the guidelines and in communication and documentation of imAEs. The EMR may also serve as a mechanism to alert other care providers that the patient is receiving immunotherapy. Specific alert mechanisms may be incorporated, such as an alert banner on the chart or a caution alert if a provider attempts to enter an order for an immune-modulating agent. A system alert can be sent to the primary oncology team if the patient presents to the emergency room, is hospitalized, or is evaluated by another discipline.

Conclusion
Nurses play a critical role in identifying imAEs, educating patients about the importance of the timely reporting of potential imAE symptoms, and assisting in the management and follow-up of patients who develop imAEs while on ICPI therapy. ICPIs are associated with a unique safety profile, characterized by fewer and more tolerable side effects than chemotherapeutic drugs. With additional indications, combination regimens, and late-stage drugs on the horizon, the clinical use of ICPIs is expected to increase. Although most imAEs are mild and easily managed, to ensure optimal patient outcomes, imAEs must be promptly identified and treated to reduce the risk of developing severe imAEs and increase the likelihood that the patient continues to receive the benefits of ICPI treatment.

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