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REVIEW

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 (ipilimumab[22]), PD-1 (nivolumab,[23] pembrolizumab[24]), and, most recently, PD-L1 (atezolizumab,[25] avelumab,[26] and durvalumab[27]). 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

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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 ICPIs approved or in late-stage development[a]

Agent	Tumor type			ORR (%)	Approved (dose)/stage of development
Anti-CTLA-4 monotherapy					
Ipilimumab	Melanoma – unresectable or metastatic (1L+)			11[22,b]	Approved[22] (3 mg/kg q3w, up to four doses)
	Melanoma with pathologic involvement of regional lymph nodes – adjuvant			49[22,c]	Approved[22] (10 mg/kg q3w, up to four doses, then q12w up to 3 years)
Anti-PD-1 monotherapy					
Nivolumab	Melanoma – unresectable or metastatic[d]	1L	*BRAF* wt	34[23]	Approved[23] (240 mg q2w)
			BRAF wt and *BRAF* mut+	40[23]	
		2L+		32[23]	
	NSCLC – metastatic (2L)	Squamous		20[23]	
		Nonsquamous		19[23]	
	Renal cell carcinoma – advanced (2L)			22[23]	
	Urothelial carcinoma – locally advanced or metastatic (2L or 1L after neoadjuvant/adjuvant chemotherapy)[e]			20[23]	
	HNSCC – recurrent or metastatic (2L)			13[23]	Approved[23] (3 mg/kg q2w)
	Classical Hodgkin lymphoma – relapsed or refractory	2L, after HSCT and brentuximab vedotin therapy[e]		66[23]	
		4L+, including prior HSCT[e]		69[23]	
	Glioblastoma			–	Phase III: CheckMate 143 (NCT02017717)
	HCC – advanced (1L)			–	Phase III: CheckMate 459 (NCT02576509)
	Gastric cancer and gastroesophageal junction cancer – unresectable advanced or recurrent			–	Phase III: NCT02267343
	SCLC – relapsed (2L)			–	Phase III: CheckMate 331 (NCT02481830)
Pembrolizumab[f]	Melanoma – unresectable or metastatic	1L		33[24]	Approved[24] (2 mg/kg q3w)
		Ipilimumab-refractory		21[24]	
	NSCLC (PD-L1+) – metastatic	1L, PD-L1+ (high levels)		45[24]	Approved[24] (200 mg q3w)
		2L, PD-L1+		18[24]	
	HNSCC – recurrent or metastatic (2L)[e]			16[24]	
	Urothelial carcinoma – locally advanced or metastatic	1L if cisplatin-ineligible[e]		29[24]	
		2L or 1L after neoadjuvant/adjuvant chemotherapy		21[24]	
	Classical Hodgkin lymphoma – relapsed or refractory, regardless of prior HSCT or brentuximab vedotin therapy (4L+)[e]			69[24]	Approved[24,103] (200 mg q3w [adults]; 2 mg/kg [up to 200 mg] q3w [pediatrics])
	MSI-H or dMMR solid tumor – unresectable or metastatic (2L+) with no satisfactory alternative treatment options[e]			40[24]	
	MSI-H or dMMR CRC – unresectable or metastatic (2L+, after treatment with fluoropyrimidine, oxaliplatin, and irinotecan)[e]			36[24]	
	TNBC – metastatic (2L and 3L)			–	Phase III: KEYNOTE-119 (NCT02555657)
	Gastric/gastroesophageal junction adenocarcinoma – unresectable, locally advanced, or metastatic (2L)			–	Phase III: KEYNOTE-061 (NCT02370498)
Anti-PD-L1 monotherapy					
Atezolizumab	Urothelial carcinoma – locally advanced or metastatic	1L if cisplatin-ineligible[c]		24[25]	Approved[25] (1200 mg q3w)
		2L or 1L after neoadjuvant/adjuvant chemotherapy[e]		15[25]	
	NSCLC – metastatic (2L)			14[13]–15[25]	

(*Continued*)

Table 1 (*Continued*)

Agent	Tumor type		ORR (%)	Approved (dose)/stage of development
Avelumab	Merkel cell carcinoma – metastatic[e]		33[26]	Approved[26] (10 mg/kg q2w)
	Urothelial carcinoma – locally advanced or metastatic (2L or 1L after neoadjuvant/adjuvant chemotherapy)[e]		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)[e]		17[27]	Approved[27] (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]
Combination anti-CTLA-4 + anti-PD-1/PD-L1				
Nivolumab + ipilimumab	Melanoma – unresectable or metastatic (1L+)[e]	*BRAF* wt	61[105]	Approved[23] (nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3w for four doses, then nivolumab 240 mg q2w)
		BRAF wt and *BRAF* mut+	50[23]	
	SCLC – extensive-stage disease (2L)		–	Phase III: CheckMate 451 (NCT02538666); NCCN recommendation[36]
	NSCLC – advanced (1L or recurrent)		–	Phase III: CheckMate 227 (NCT02477826)
	Glioblastoma		–	Phase III: CheckMate 143 (NCT02017717)
Durvalumab + tremelimumab[g]	NSCLC – locally advanced or metastatic (1L and 3L)		–	Phase III: MYSTIC (NCT02453282), ARCTIC (NCT02352948)
	HNSCC – recurrent/metastatic (1L and 2L)		–	Phase III: KESTREL (NCT02551159), EAGLE (NCT02369874)
	Urothelial carcinoma – unresectable (1L)		–	Phase III: DANUBE (NCT02516241)

Notes: [a]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. [b]Best overall response rate. [c]Recurrence-free survival rate. [d]Accelerated approval for BRAF V600 mutation-positive unresectable/metastatic melanoma; continued approval may be contingent on confirmatory trials. [e]Accelerated approval; continued approval may be contingent on confirmatory trials. [f]Pembrolizumab is also approved in combination with pemetrexed and carboplatin as 1L treatment for metastatic nonsquamous NSCLC (ORR, 55%).[24] [g]Tremelimumab is an anti-CTLA-4 monoclonal antibody currently in late-stage studies in combination with durvalumab.

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.

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.[37,38]

ICPIs have improved the prognosis for patients with advanced melanoma,[2,4,9,39–42] non-small cell lung cancer (NSCLC),[6,11,13,16,21,43,44] renal cell carcinoma,[5] urothelial carcinoma,[7,8,15,18–20] Hodgkin's lymphoma,[14,45] head and neck squamous cell carcinoma,[3,12] Merkel cell carcinoma,[10] and microsatellite instability – high or mismatch repair-deficient cancer.[1] Given the current success of ICPIs in an increasingly wide range of tumor types, the approved indications for ICPIs are expected to increase. In fact, ICPIs have shown promising efficacy in clinical studies in many other cancer types including small cell lung cancer,[31] hepatic cancer,[33] triple-negative breast cancer,[28] ovarian cancer,[32] colorectal cancer,[46] gastric cancer,[29] and glioblastoma.[30]

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.[47,48] 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[27]). 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 + tremelimumab[56]). 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%, pembrolizumab[16,20]) or anti-PD-L1 (5–7%, atezolizumab;[7,17] 2%, durvalumab;[59] 1–2%, avelumab[10,61]) 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%).[4,9] 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).[57] 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 dermatological 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%];[4,9,39,42] 10 mg/kg [rash, 34%; pruritus, 40%][40]) than with anti-PD-1 (nivolumab/pembrolizumab: rash, 4–22%; pruritus, 2–23%)[2,4,6,11,15,16,41–43,50,51,62] 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%).[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)[22,57] 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%;[4,6,11,15,41,62] 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[a]

Adverse events	Melanoma								NSCLC				UC			
	Standard-dose anti-CTLA-4[b,4,9,39]		High-dose anti-CTLA-4[c,22,40]		Anti-PD-1[d,2,4,41,42,51,62]		Anti-CTLA-4 + anti-PD-1[e,4,9]		Anti-PD-1[d,6,11,16,43,50,95]		Anti-PD-L1[f,13,25,44]		Anti-PD-1[g,15,18,20,95]		Anti-PD-L1[h,7,25,27,59–61]	
Grade	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4
Dermatologic, %																
All	44–63	0–3	63	5	29–42	<1–2	59–73	6–9	9	0	NR	NR	17	1	1	1
Rash	19–30	0–2	34	1	2–22	0–1	28–43	3–4	5–11	<1	NR	NR	7	1	1–7	<1–1
Pruritus	24–35	0–<1	40	2	2–22	0–1	33–40	1–2	2–11	0	NR	NR	9–20	0	1	<1
Gastrointestinal, %																
All	29–37	8–12	46	16	12–20	1–2	46–49	15–20	8	1	NR	NR	9	2	NR	NR
Diarrhea	28–35	5–11	41	10	2–19	0–2	44–45	9–10	8–14	0–4	1[i]	<1[i]	2–3[i]	1–2[i]	<1–2	0–<1
Colitis	8–12	2–9	16	8	1–3	1–2	12–18	8–13	1–2	<1–1					1	0–1
Endocrine, %																
All	8–15	2–4	38	9	7–14	0–1	30–31	5	NR	NR	NR	NR	14	<1	NR	NR
Hypothyroidism	2–13	0	9	<1	2–9	0–<1	15–17	0–<1	4–9	0–<1	4	<1	6–11	0	3–6	0–<1
Hyperthyroidism	1	0	NR	NR	2–5	0	10	1	1–8	0–<1	1	0	2–4	0	1–5	0
Hypopituitarism	2	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hypophysitis	2–7	2–4	18	5	1	0–1	8–13	2	<1–1	<1–1	NR	NR	1	<1	<1	NR
Adrenal insufficiency	2	0	NR	NR	1	1	5	1	<1–1	<1	NR	NR	<1–1	0–<1	1	0
Diabetes mellitus	NR	NR	NR	NR	<1–1	0–<1	NR	NR	0–1	0–1	<1	NR	<1	0	<1	NR
Hepatic, %																
All	4–9	0–2	25	11	3–6	1–3	30–32	13–19	2	0	NR	NR	4	2	2	1
AST increased	1–9	0–1	20	5	1–4	0–1	15–28	6–7	2–3	0–1	4	2	NR	NR	<1–1	<1
ALT increased	2–9	0–2			1–4	0–1	18–26	8–11	2–4	0–<1	4	2	NR	NR	1	NR
Hepatitis	0–1	0	16[i]	11	1	0–1	2	2	<1	<1	1	0–1	1	<1	1–2	1
Pulmonary, %																
All	2	0–<1	NR	NR	2	0–1	7–11	1–2	NR	NR	NR	NR	4	1	NR	NR
Pneumonitis	2	0–<1	<1	NR	1–2	0–1	6–10	1–2	3–6	1–3	4	2	2–4	1–2	1	0–<1
Renal, %	2	0	NR	NR	1–2	0–1	3	1	1–3	<1–1	NR	NR	1	<1–1	0–1	0–1
Neurologic, %	NR	NR	5	2	NR	NR	NR	NR	<1	<1	NR	NR	NR	NR	NR	NR

Notes: [a]Pivotal trials that led to US FDA approval. [b]Ipilimumab 3 mg/kg. [c]Ipilimumab 10 mg/kg. [d]Nivolumab 3 mg/kg or pembrolizumab 2–10 mg/kg. [e]Ipilimumab 3 mg/kg + nivolumab 1 mg/kg. [f]Atezolizumab 1200 mg. [g]Nivolumab 3 mg/kg or pembrolizumab 200 mg. [h]Atezolizumab 1200 mg or durvalumab 10 mg/kg or avelumab 10 mg/kg. [i]Does not include Grade 1. [j]Diarrhea and/or colitis.

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[a]

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

(*Continued*)

Table 3 (*Continued*)

Organ	ImAE	Symptoms	Evaluation	Grading[b]	Management
Endocrine (HPA axis)	Hypophysitis Adrenal insufficiency Adrenal crisis	Hypophysitis: visual changes, headaches, fatigue, weakness, confusion, hallucinations, memory loss, labile mood, insomnia, anorexia Adrenalitis: fatigue, malaise, hypotension, vague gastrointestinal symptoms, weight loss, hypoglycemia	Hypophysitis: Hormone levels: ACTH, FSH, LH, prolactin, ADH, oxytocin, testosterone Laboratory: CBC and blood cultures to r/o sepsis Diagnostic evaluation Pituitary scan MRI of brain with pituitary Endocrinology consult Adrenalitis: Hormone levels: cortisol, ACTH, cosyntropin stimulation test, aldosterone If am cortisol <3 μg/dL: adrenal insufficiency Primary adrenal insufficiency: low cortisol, high ACTH Secondary adrenal insufficiency: low cortisol, low ACTH Endocrinology consult	Grade 1: Asymptomatic Grade 2: Symptomatic Grade 3–4: Severe symptoms Requiring hospitalization or urgent medical intervention Limiting self-care ADL Life-threatening	Grade 1: Continue ICPI Grade 2–4: Hold ICPI Hypophysitis[q] Stress dose IV MPS with mineral corticoid if also adrenal crisis Hormone repletion Adrenalitis Hormone repletion (may require lifetime hormone replacement) Requirement for stress dosing of steroid If imAE resolves to Grade 1 or less, taper steroid dose over 4–6 weeks and consider resuming ICPI[h]
Hepatic	Elevated AST/ALT Elevated bilirubin Hepatitis	Nausea Decreased appetite Fever Vague abdominal discomfort RUQ pain Dehydration Jaundice Bleeding, bruising Dark urine	Laboratory: liver enzymes (AST, ALT, ALK, total and direct bilirubin) every 3 days, coagulation panel Diagnostic evaluation: Liver ultrasound Gastroenterology consult Hepatology consult Consider liver biopsy to confirm diagnosis	Grade 1: AST or ALT > ULN to 3 × ULN and/or total bilirubin > ULN to 1.5 × ULN Grade 2: AST or ALT >3 × to <5 × ULN and/or total bilirubin >1.5–3 × ULN Grade 3–4: AST or ALT >5 × ULN and/or total bilirubin >3 × ULN	Grade 1: Continue ICPI Stop hepatotoxic medications Grade 2: Hold ICPI[e,g] Monitor laboratory results (eg, 3× per week) Consider MPS 0.5–1.0 mg/kg/day If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks[o,r] Grade 3–4: Permanently discontinue ICPI[s,h] MPS 1–2 mg/kg/day with taper as listed for Grade 2 Refractory/recurrent: Consider additional immunosuppressant (eg, mycophenolate mofetil)

(*Continued*)

Table 3 (*Continued*)

Organ	ImAE	Symptoms	Evaluation	Grading[b]	Management
Pulmonary	Ground glass opacities on imaging Pneumonitis Sarcoid-like lung disease	Dry cough Wheezing Tachypnea/tachycardia Shortness of breath at rest Shortness of breath at exertion Hypoxia Increased oxygen requirements Chest pain Radiographic changes	Oxygen saturation at rest and with ambulation Laboratory: CBC Rule out: Infectious cause Lymphangitic spread Pulmonary embolism Pleural effusion Consult: Interventional pulmonology Infectious disease Diagnostics: CT scan Bronchoscopy with biopsy PFTs	Grade 1: Asymptomatic Clinical or diagnostic observations Grade 2: Mild-to-moderate symptoms, limiting instrumental ADLs Medical intervention indicated Grade 3–4: Severe symptoms limiting self-care ADLs New or worsening hypoxia Life-threatening urgent intervention indicated	Grade 1: Consider holding ICPI Oxygen support; albuterol nebulizer, PRN; steroid inhaler, PRN Monitor every 2–3 days Grade 2: Hold ICPI[e,g] MPS 1–2 mg/kg/day Daily monitoring If imAE resolves to baseline, consider resuming treatment after steroid tapered over 4–6 weeks[f,h] Grade 3–4: Permanently discontinue ICPI MPS 1–2 mg/kg/day increasing to 2–4 mg/kg/day if needed; taper as listed for Grade 2 Refractory: Consider additional immunosuppressant (eg, infliximab)
Renal	Interstitial nephritis Granulomatous nephritis Glomerular lupus-like nephropathy Renal insufficiency Renal failure	Often asymptomatic Increase in serum creatinine Vague nausea Emesis Decreased urine output Cloudy/dark urine Blood in urine Ankle swelling	Laboratory: serum creatinine, urinalysis Nephrology consult Renal ultrasound Renal biopsy	Grade 1: Creatinine level increased >0.3 mg/dL; creatinine 1.5–2.0 > baseline Grade 2: Creatinine 2.3 × above baseline Grade 3: Creatinine >3 × baseline or >4.0 mg/dL Grade 4: Life-threatening	Grade 1: Continue ICPI Hold all nephrotoxic drugs Hydration Grade 2–3: Hold ICPI[e,g,t] 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 If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks[f,h] Grade 4: Permanently discontinue ICPI MPS 1–2 mg/kg/day with taper as listed for Grade 2–3
Pancreatic	Elevated amylase and lipase Pancreatitis Type 1 diabetes mellitus	May be asymptomatic RUQ abdominal pain Nausea Vomiting Increase in stool frequency, bulk, or odor Steatorrhea	Laboratory: amylase and lipase levels, blood glucose Pancreatic ultrasound CT scan Gastroenterology consult Endoscopy	Grade 1: Lipase > ULN–1.5 × ULN Grade 2: Lipase 1.5–2 × ULN Grade 3: >2–5 × ULN Grade 4: >5 × ULN	Grade 1: Continue ICPI Monitor laboratory results at least weekly Grade 2–3: Hold ICPI[e,g,u] MPS 0.5–1.0 mg/kg/day If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks[f] Grade 4: Permanently discontinue ICPI[v,w] MPS 1–2 mg/kg/day with taper as for Grade 2–3

(*Continued*)

Table 3 (*Continued*)

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

(*Continued*)

Table 3 (*Continued*)

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

(*Continued*)

Table 3 (*Continued*)

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

Notes: [a]Based on published management algorithms[22–27,88,93–97] and authors' clinical experience. [b]Grading based on NCI Common Terminology Criteria for Adverse Events v4.0. [c]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. [d]For Imfinzi (durvalumab): hold ICPI if Grade 2 for >1 week. [e]For Yervoy (ipilimumab): permanently discontinue if Grade 2 imAE persists ≥6 weeks or unable to reduce prednisone to ≤7.5 mg prednisone or equivalent per day or to complete four-dose course within 16 weeks. [f]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. [g]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. [h]For Imfinzi (durvalumab): resume treatment when imAE resolves to Grade ≤1 and corticosteroid dose has been reduced to <10 mg prednisone or equivalent per day. [i]For Yervoy (ipilimumab): initiate 0.5 mg/kg/day prednisone or equivalent if symptoms persist >1 week, worsen, or recur. [j]For Yervoy (ipilimumab) or combination Yervoy + Opdivo (ipilimumab + nivolumab): permanently discontinue. [k]Permanently discontinue Imfinzi (durvalumab) for Grade 3 gastrointestinal imAE. [l]Permanently discontinue Bavencio (avelumab) if Grade 3 imAE is recurrent. [m]For Tecentriq (atezolizumab): resume treatment when imAE resolves to Grade 1 or less and is controlled with ≤10 mg/kg prednisone or equivalent per day. [n]Keytruda (pembrolizumab) may be continued in cases of Grade 2 hyperthyroidism and all-grade hypothyroidism. [o]For Opdivo (nivolumab): no recommended dose modifications for hypothyroidism or hyperthyroidism. [p]For Bavencio (avelumab): no recommended dose modifications for Grade 2 endocrinopathies. [q]For Tecentriq (atezolizumab): permanently discontinue for Grade 4 hypophysitis. [r]Begin taper if AE improves to Grade 2 for Opdivo (nivolumab) or if liver function tests improve for Yervoy (ipilimumab). [s]Permanently discontinue Imfinzi (durvalumab) 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. [t]Permanently discontinue Yervoy (ipilimumab), Keytruda (pembrolizumab), or Imfinzi (durvalumab) for Grade 3 nephritis. [u]Permanently discontinue Yervoy (ipilimumab) for Grade 3 pancreatitis. Discontinue Keytruda (pembrolizumab) or Opdivo (nivolumab) if recurrent Grade 2 or 3. [v]For grade 4 serum amylase or lipase elevation, hold Tecentriq (atezolizumab) and consider resuming treatment once imAE resolves to Grade ≤1 within 12 weeks and corticosteroids reduced to ≤10 mg/day oral prednisone. [w]Hold Imfinzi (durvalumab) for Grade 2–4 type 1 diabetes mellitus; resume treatment if type 1 diabetes mellitus resolves to Grade ≤1. [x]Permanently discontinue Yervoy (ipilimumab) if Grade ≥2 or Grade 1 not responding to steroids within 2 weeks or requiring systemic therapy. [y]Permanently discontinue Opdivo (nivolumab), Keytruda (pembrolizumab), Tecentriq (atezolizumab), or Bavencio (avelumab) if Grade 3. [z]For Tecentriq (atezolizumab): permanently discontinue for any grade meningitis or encephalitis and treat with steroids (MPS, 1–2 mg/kg/day); use medical intervention as appropriate for myasthenic syndrome/myasthenia gravis or Guillain–Barre syndrome. [A]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; Hgl, 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; PFTs, pulmonary function tests; Plt, 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.

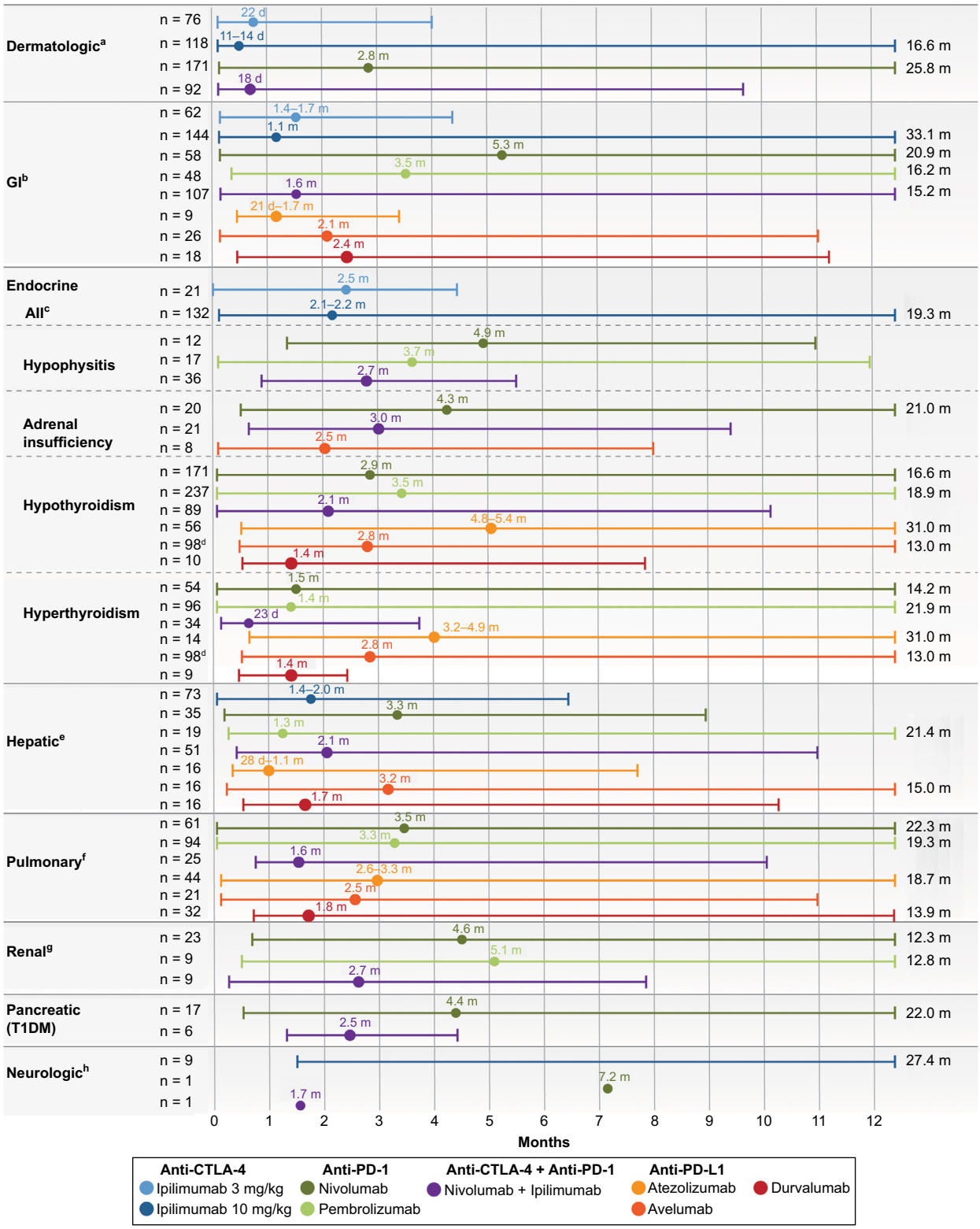

Figure 1 Time to onset of immune-mediated toxicities (median and range).[22–27]

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). [a]Dermatitis in ipilimumab studies; immune-mediated rash in nivolumab and nivolumab + ipilimumab studies. [b]Enterocolitis in ipilimumab studies; colitis in nivolumab, pembrolizumab, avelumab, and nivolumab + ipilimumab studies; colitis or diarrhea in atezolizumab and durvalumab studies. [c]Includes hypopituitarism, adrenal insufficiency, hypothyroidism, hyperthyroidism, hypogonadism, thyroiditis, Cushing's syndrome, and Graves' ophthalmopathy. [d]Hypothyroidism and hyperthyroidism are combined for avelumab. [e]Hepatitis. [f]Pneumonitis. [g]Nephritis or renal dysfunction in nivolumab and nivolumab + ipilimumab studies; nephritis in pembrolizumab studies. [h]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.

durvalumab, 2%[59]), and 44–45% of patients receiving combination anti-CTLA-4 and anti-PD-1 therapy with ipilimumab and nivolumab.[4,9] Colitis has been observed in 7–16% of patients receiving anti-CTLA-4 therapy (ipilimumab: 3 mg/kg, 7–12%;[4,9,39,42] 10 mg/kg, 16%[40]), 1–3% of patients treated with anti-PD-1/PD-L1 antibodies (1% for nivolumab,[4,6,11,41,62] atezolizumab,[7,13,17,44] and durvalumab;[59] avelumab, 2%;[26] pembrolizumab, 1–3%[2,16,18,20,42,43]), and 12–18% of patients treated with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).[4,9] Rates of Grade 3/4 diarrhea or colitis are low (≤4%) in patients receiving anti-PD-1 or anti-PD-L1 monotherapy,[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%)[4,9,39,40,42] or combination anti-CTLA-4 and anti-PD-1 therapy with nivolumab and ipilimumab (8–13%).[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).[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.[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.[22–27] Rates of all-grade endocrinopathies are generally low in patients receiving anti-PD-1/PD-L1 monotherapy, with <10% of patients experiencing each individual endocrinopathy.[23–27] Higher rates are reported in patients treated with anti-CTLA-4 therapy either as monotherapy (ipilimumab 3 mg/kg, 8–15%;[4,9,39] ipilimumab 10 mg/kg, 38%[40]) or in combination with anti-PD-1 therapy (ipilimumab + nivolumab, 30–31%[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%;[22] anti-PD-1/PD-L1: nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab, <1%[4,24–27] for each individual endocrinopathy); however, higher rates have been reported with high-dose anti-CTLA-4 (ipilimumab 10 mg/kg, 8%)[22] and combination anti-CTLA-4 and anti-PD-1 (ipilimumab + nivolumab, 5%).[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;[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),[23–25,27] but has been observed in 2–7% of patients receiving anti-CTLA-4 therapy (ipilimumab) at the 3 mg/kg dose[4,9,42] and 18% of patients receiving the 10 mg/kg dose,[40] and in 8–13% of patients treated with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).[4,9] The vast majority of patients who experience Grade ≥2 hypophysitis fail to recover pituitary function and require lifelong hormone replacement therapy.[22,57,68] Adrenal insufficiency can arise secondary to hypopituitarism (≤1%, anti-PD-1 monotherapy [nivolumab][23] or anti-PD-L1 monotherapy [atezolizumab,[25] avelumab,[26] durvalumab[27]]; 5%, combination anti-CTLA-4 and anti-PD-1 [ipilimumab + nivolumab][23]), typically manifesting as dehydration, hypotension, hyponatremia, and/or hyperkalemia similar to sepsis syndrome.[69]

Hypothyroidism has been reported in 9% of patients treated with anti-PD-1 (nivolumab or pembrolizumab)[23,24] or high-dose anti-CTLA-4 monotherapy (ipilimumab 10 mg/kg),[40] in 2–13% of patients receiving standard-dose anti-CTLA-4 monotherapy (ipilimumab 3 mg/kg),[4,9,39,42] in 4–5% of patients treated with anti-PD-L1 antibodies (atezolizumab, 4%;[25] avelumab, 5%;[26] durvalumab, 6%[27]), and in 15–17% of patients receiving combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).[4,9] In clinical registration studies, the median onset of hypothyroidism ranged from 1 to 5 months,[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.[23–27,47,70] Hyperthyroidism, which is less common than hypothyroidism, resolves in the vast majority of patients.[71]

Hepatic

Hepatotoxicity, including hepatitis and elevated alanine transaminase (ALT)/aspartate transaminase (AST), has been documented in patients treated with ICPIs.[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)[4,9,39] to 25% (ipilimumab 10 mg/kg),[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)[4,6,11,15,41,62] and in 30–32% (13–19% Grade 3/4) of the patients receiving combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).[4,9] Immune-mediated hepatitis, reported in ≤2% of patients treated with ICPI monotherapy[23–27,39] (excluding ipilimumab 10 mg/kg dose, 15%),[22] typically presents

at 1–3 months and resolves with steroid treatment in most patients (Figure 1).[22–27] Although rare, fatal cases of immune-mediated hepatitis have occurred with ICPI monotherapy (0.2%, ipilimumab 3 mg/kg;[22] 0.1%, avelumab;[26] 0.5%, durvalumab[27]). Elevated ALT/AST with concomitant elevated bilirubin may indicate a more serious hepatic injury.[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),[22] in 1–3% of those receiving anti-PD-1/PD-L1 (nivolumab, pembrolizumab, or atezolizumab, 3%;[23–25] avelumab, 1%;[26] durvalumab, 0.5%[27]), and in 6% of those receiving combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).[23] Immune-mediated pneumonitis has been reported more frequently in patients receiving anti-PD-1 therapy (nivolumab or pembrolizumab) for NSCLC (3–6%)[6,11,16,43,50] than for melanoma (1–2%; Table 2).[2,4,41,42,62,66] Pneumonitis has a median onset ranging from 2 months to 4 months (Figure 1).[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).[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.[23]

Renal

Immune-mediated nephritis has been observed at low rates in patients receiving anti-CTLA-4 therapy (ipilimumab, <1%),[22] anti-PD-1 antibodies (nivolumab, 1.2%;[23] pembrolizumab, <0.3%[24]), anti-PD-L1 antibodies (avelumab, 0.1%;[26] durvalumab, ≤1%[27]), and combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab; 2.2%).[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).[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[23–26] (excluding anti-CTLA-4 therapy with ipilimumab 10 mg/kg, 1.3%)[22] or combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).[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%)[23,24] and anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab, ≤0.3%),[25–27] and in 1.5% of patients treated with combination anti-CTLA-4 and anti-PD-1 therapy (ipilimumab + nivolumab).[23] Although diabetes mellitus was not observed in clinical trials of anti-CTLA-4 monotherapy (ipilimumab),[22] a report has described a case of diabetes insipidus associated with anti-CTLA-4 monotherapy (ipilimumab).[75]

Ocular

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

Musculoskeletal

Musculoskeletal imAEs have been reported at low rates in ICPI clinical studies, including polymyalgia rheumatica (<1%), myositis (≤1%), and arthritis (<2%).[22–24,26,27] Although inflammatory arthritis has been reported with ICPI treatment in case series,[76,77] the rate of this adverse event remains unclear due to inconsistent reporting of inflammatory arthritis in ICPI clinical studies.[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, neuropathy, and nerve paresis. In clinical trials, these neurologic imAEs occurred in ≤1% of patients.[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).[79]

Cardiovascular

Cardiovascular imAEs occurred in ≤1% of patients treated with ICPIs in clinical studies, including myocarditis, pericarditis, vasculitis, and heart failure.[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.[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).[82–85]

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 v4.0[88] 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 tools[86,93–96,100] 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.

Table 4 ICPI imAE management resources

Resource	URL
Print/online	
Immune-mediated adverse reactions management guide for Yervoy[94]	www.hcp.yervoy.com/servlet/servlet.FileDownload?file=00Pi000000TUzayEAD
Immune-mediated adverse reactions management guide for Opdivo monotherapy and Opdivo + Yervoy[95]	www.opdivohcp.com/servlet/servlet.FileDownload?file=00Pi000000kLoKcEAK
Opdivo safety tool[100]	www.opdivosafetytool.com/#/signs-symptoms-management-imars
A guide to monitoring patients during treatment with Keytruda[93]	www.keytruda.com/static/pdf/adverse-reaction-management-tool.pdf
A nurse's guide to Keytruda[99]	www.keytruda.com/static/pdf/nurse-guide-to-treatment-monitoring.pdf
Tecentriq adverse event management brochure[96]	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 tool[86]	www.clinicaloptions.com/immuneaetool
Yervoy Risk Evaluation Mitigation Survey[91]	www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm249435.pdf
Imfinzi Immune-Mediated Adverse Events Management Handbook[97]	www.imfinzi.com/content/dam/website-services/us/423-durva0-com/resources/imAE_management_handbook.pdf
Lighthouse[106]	www.lighthouseprogram.com
Published literature	
Ipilimumab and its toxicities: a multidisciplinary approach[92]	www.ncbi.nlm.nih.gov/pubmed/23774827
Management of immune-related adverse events and kinetics of response with ipilimumab[57]	www.ncbi.nlm.nih.gov/pubmed/22614989
Management of adverse events following treatment with anti-programmed death-1 agents[58]	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.

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.[57,92] Patients on prolonged corticosteroid treatment (>20 mg prednisone equivalent daily for 4 weeks) may require supportive therapy with a proton pump inhibitor and/or antibiotic prophylaxis.[58,101] In those patients who require long-term steroid use, evaluation by an endocrinologist is recommended, as additional management such as bone density monitoring may be necessary to evaluate the risk of steroid-induced osteoporosis and diabetes and the need for calcium/vitamin D_3 repletion.[102] In general, if a patient requires >10 mg/day of prednisone equivalent for >12 weeks or if there is a persistent Grade 2 or 3 imAE for >12 weeks, then ICPI should be permanently discontinued.[57,58,91–97] The diagnosis and management of three sample patients with different imAEs are shown in Figure 2, including rash, colitis, and adrenal insufficiency.

Education of patients, caregivers, and health care 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

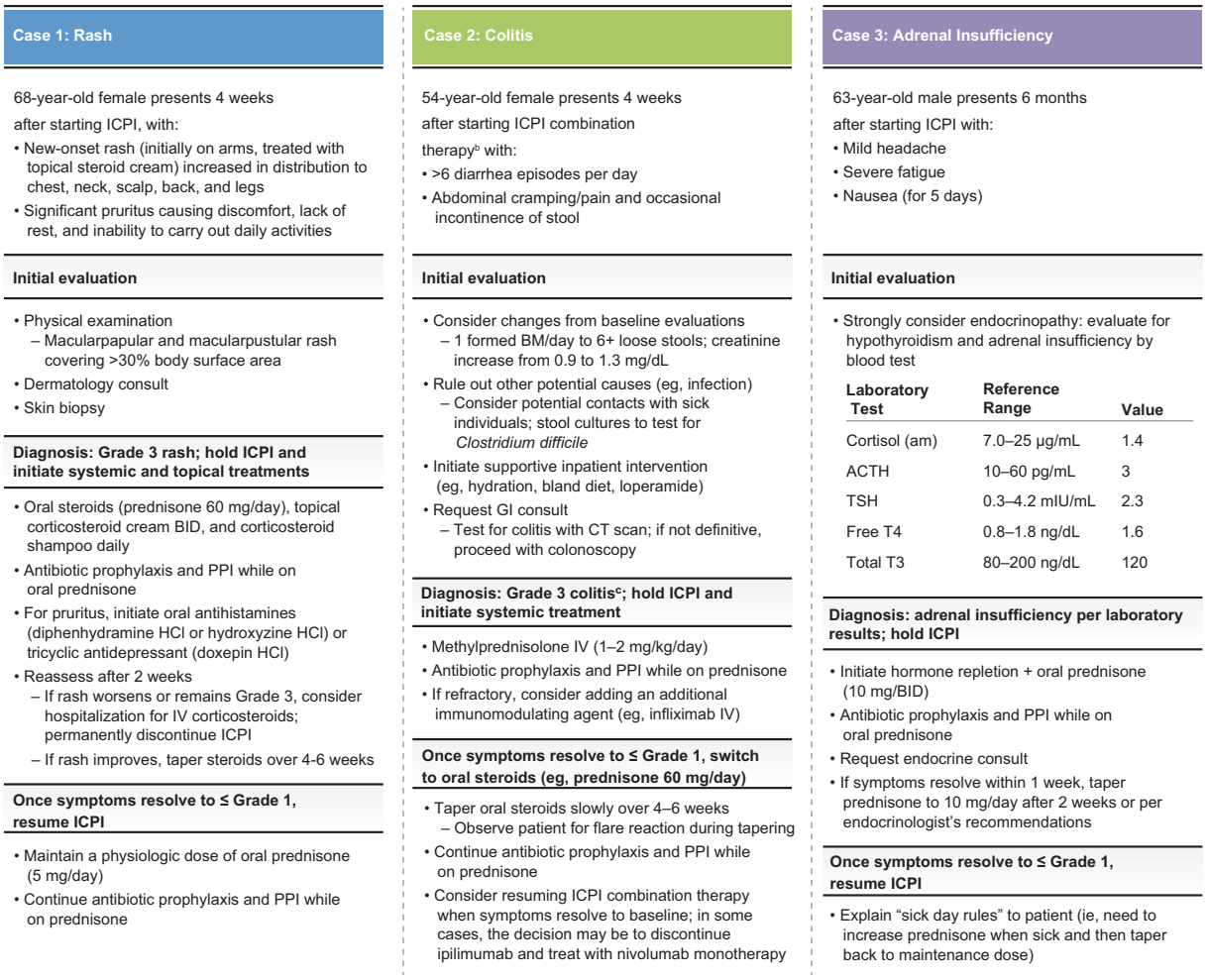

Figure 2 Sample imAE case management.[a]
Notes: [a]Cases based on fictitious patients. [b]Ipilimumab + nivolumab. [c]Permanently discontinue ICPI therapy in patients with Grade 4 colitis.
Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice daily; BM, bowel movement; CT, computerized tomography; GI, gastrointestinal; HCl, hydrochloride; ICPI, immune checkpoint inhibitor; imAE, immune-mediated adverse event; IV, intravenous; PPI, protein pump inhibitor; TSH, thyroid-stimulating hormone.

mycophenolate mofetil) may be used.[57,58] It is critical that oncology nurses and physicians treating patients receiving ICPIs familiarize themselves with the signs and symptoms of serious imAEs (Table 3).

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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