

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

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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 I 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	Approved ²³ (3 mg/kg q2w)		
		Nonsquamous	19 ²³			
	Renal cell carcinoma – advanced (2L)				22 ²³	Approved ²³ (3 mg/kg q2w)
	Urothelial carcinoma – locally advanced or metastatic (2L or 1L after neoadjuvant/adjuvant chemotherapy) ^e				20 ²³	
	HNSCC – recurrent or metastatic (2L)			13 ²³		
	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		Approved ^{24,103} (200 mg q3w [adults]; 2 mg/kg [up to 200 mg] q3w [pediatrics])	
		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		
	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	Phase III: KEYNOTE-119 (NCT02555657)	
	TNBC – metastatic (2L and 3L)			–		
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 I (Continued)

Agent	Tumor type	ORR (%)	Approved (dose)/stage of development
Avelumab	Merkel cell carcinoma – metastatic ^c	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	Approved ²³ (nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3w for four doses, then nivolumab 240 mg q2w)
		BRAF wt and BRAF mut+	
	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: ^aLate-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. ^bBest overall response rate. ^cRecurrence-free survival rate. ^dAccelerated approval for BRAF V600 mutation-positive unresectable/metastatic melanoma; continued approval may be contingent on confirmatory trials. ^eAccelerated approval; continued approval may be contingent on confirmatory trials. ^fPembrolizumab is also approved in combination with pemetrexed and carboplatin as 1L treatment for metastatic nonsquamous NSCLC (ORR, 55%). ^gTremelimumab 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/kg²⁷). 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%, 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-L1 ^{d,2,4,41,42,51,62}			Anti-CTLA-4 + anti-PD-L1 ^{e,4,9}			Anti-PD-L1 ^{f,13,25,44}			Anti-PD-L1 ^{g,15,18,20,95}			Anti-PD-L1 ^{h,7,25,27,59,61}		
	All	3/4	All	All	3/4	All	All	3/4	All	All	3/4	All	All	3/4	All	All	3/4	All	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	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	<1	<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	<1	<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	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 ^j	1-2 ^j	<1-2	0-<1	0-1	0-1	0-1	0-1	
	Colitis	8-12	2-9	16	8	1-3	1-2	12-18	8-13	1-2	<1-1					1	0-1	0-1	0-1	0-1	
	Endocrine, %	All	8-15	2-4	38	9	7-14	0-1	30-31	5	NR	NR	NR	14	<1	NR	NR	NR	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	0	0	0	0	
	Hyperthyroidism	1	0	NR	NR	2-5	0	10	1	1-8	0-<1	1	0	2-4	0	1-5	0	0	0	0	
	Hypopituitarism	2	2	NR	NR	NR	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	<1	<1	<1	<1	
Adrenal insufficiency	2	0	NR	NR	1	1	5	1	<1-1	<1	NR	NR	<1-1	0-<1	1	0	0	0	0	0	
	Diabetes mellitus	NR	NR	NR	NR	<1-1	0-<1	NR	NR	0-1	0-1	<1	NR	<1	<1	0	<1	<1	<1	<1	
Hepatic, %	All	4-9	0-2	25	11	3-6	1-3	30-32	13-19	2	0	NR	NR	4	2	2	1	1	1	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	<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	NR	NR	NR	
	Hepatitis	0-1	0	16 ⁱ	11	1	0-1	2	2	<1	<1	1	0-1	1	<1	1-2	1	1	1	1	
Pulmonary, %	All	2	0-<1	NR	NR	2	0-1	7-11	1-2	NR	NR	NR	NR	4	1	NR	NR	NR	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	0-<1	0-<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	0-1	0-1	0-1	
	Neurologic, %	NR	NR	5	2	NR	NR	NR	NR	<1	<1	NR	NR	NR	NR	NR	NR	NR	NR	NR	

Notes: ^aPivotal trials that led to US FDA approval. ^bIpilimumab 3 mg/kg. ^cIpilimumab 10 mg/kg. ^dNivolumab 3 mg/kg or pembrolizumab 2-10 mg/kg. ^eIpilimumab 3 mg/kg + nivolumab 1 mg/kg. ^fAtezolizumab 1200 mg. ^gNivolumab 3 mg/kg or pembrolizumab 200 mg. ^hAtezolizumab 1200 mg or durvalumab 10 mg/kg or avelumab 10 mg/kg. ⁱDoes not include Grade 1. ^jDiarrhea 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	Maculopapular rash	Rule out: Cellulitis	Grade 1–2:	Grade 1–2: Continue ICPI ^{c,d}
	Pruritus	Pruritus	Contact dermatitis	Covers ≤30% of body surface area	Start topical steroid cream, anti-itch cream, oral antihistamine; cold compresses, oatmeal baths
	Erythema	Hair color changes	Drug reaction	±Pruritus	If rash persists for >1 week or interferes with daily living, start moderate potency steroid cream ^c
	Dry mouth	Skin discoloration	Sun exposure	Grade 3–4:	Grade 3: If serious or with desquamation, hold ICPI
	Vitiligo (hair, skin)	Skin peeling, blisters	Radiation recall	≤30% of body surface area	Start MPS 1.0–2.0 mg/kg/day
	Stevens–Johnson syndrome	Oral ulcerations	Laboratory: CBC	±Pruritus	If imAE resolves to Grade 1 or less, taper steroid dose over 4–6 weeks and consider resuming ICPI ^{e–h}
	Toxic epidermal necrolysis	Eosinophil infiltrates	Dermatology consult	Limits self-care ADLs	Grade 4: Permanently discontinue ICPI
		Epidermal spangiosis	Confirmatory testing: skin biopsy	Life-threatening consequences	Start steroid followed by tapering as for Grade 3
		Lichenoid deposits			Grade 2: Hold ICPI until Grade 1 ^{e,f,h,i}
Gastrointestinal	Diarrhea	Abdominal pain	Determine frequency and volume of stool	Grade 1:	If recurrent or if lasting >5 days, ^f consider starting steroid dose (prednisone 1.0–2.0 mg/kg/day or equivalent) ^g
	Colitis	Cramping	Laboratory: CBC and CMP	<4 stools over baseline	Grade 3: Hold ICPI ^{g,h,i,k,l}
	Enterocolitis	Change in bowel pattern	Send stool sample for:	Asymptomatic	Start MPS 1.0–2.0 mg/kg/day
	Nausea	Increase in ostomy output	WBC (r/o inflammation)	Grade 2:	If imAE resolves to Grade 1 or less, taper steroid dose over 4–6 weeks and consider resuming ICPI ^{im}
	Vomiting	Mucous or blood in stool	C&S and <i>Clostridium difficile</i> (r/o infection)	4–6 stools over baseline	Grade 4: Permanently discontinue ICPI
	Gastritis	Incontinence	Diagnostic testing:	IV fluids <24 hours indicated	Start steroid followed by tapering as for Grade 3
	Ischemic gastritis	Peritoneal signs	Abdominal ultrasound	Colitis with abdominal pain, blood in stool, no ADL interference	Refractory:
	GI perforation		Abdominal CT scan	Grade 3:	Consider additional immunosuppressant (eg, infliximab)
	Perforation sepsis		Gastroenterology consult	≥7 stools/day over baseline	
	Ileus		Confirmatory testing:	IV fluids >24 hours	
			Endoscopy	Interference with ADLs	
			Colonoscopy	Severe abdominal pain, peritoneal signs; medical intervention indicated	
Endocrine (thyroid)				Grade 4:	
				Life-threatening perforation	
				Grade 1:	Grade 1: Continue ICPI
				Asymptomatic	Grade 2–4: Hold ICPI ^{m–p}
				Grade 2:	Manage symptoms
				Symptomatic	Hypothyroidism
				Requiring hormone replacement or medical intervention	Medical management for severe symptoms
				Grade 3–4:	Hypothyroidism
				Severe symptoms, life-threatening	Initiate hormone replacement if TSH >10
				Requiring hospitalization or urgent medical intervention	Adjust replacement hormone dosing to maintain T4 in mid-range
				Limiting self-care ADL	Consider resuming ICPI when symptoms resolve to ≤Grade 1

(Continued)

Table 3 (Continued)

Organ	ImAE	Symptoms	Evaluation	Grading ^b	Management
Endocrine (HPA axis)	Hypophysitis	Hypophysitis: visual changes, headaches, fatigue, weakness, confusion, hallucinations, memory loss, labile mood, insomnia, anorexia	Hypophysitis: Hormone levels: ACTH, FSH, LH, prolactin, ADH, oxytocin, testosterone Laboratory: CBC and blood cultures to r/o sepsis	Grade 1: Asymptomatic Grade 2: Symptomatic Grade 3–4: Severe symptoms	Grade 1: Continue ICPI Grade 2–4: Hold ICPI Hypophysitis ^a Stress dose IV MPS with mineral corticoid if also adrenal crisis Hormone repletion
	Adrenal insufficiency Adrenal crisis	Adrenalitis: fatigue, malaise, hypotension, vague gastrointestinal symptoms, weight loss, hypoglycemia	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	Requiring hospitalization or urgent medical intervention Limiting self-care ADL Life-threatening	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 ^b
Hepatic	Elevated AST/ALT Elevated bilirubin Hepatitis	Nausea Decreased appetite Fever Vague abdominal discomfort RUQ pain Dehydration Jaundice Bleeding, bruising Dark urine	Endocrinology consult 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 ^{eg} 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 ^{or} Grade 3–4: Permanently discontinue ICPI ^{sh} 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	Dry cough	Oxygen saturation at rest and with ambulation	Grade 1:	Grade 1: Consider holding ICPI
	Pneumonitis	Wheezing	Laboratory: CBC	Asymptomatic	Oxygen support; albuterol nebulizer, PRN;
	Sarcoid-like lung disease	Shortness of breath at rest	Rule out:	Grade 2:	steroid inhaler, PRN
		Shortness of breath at exertion	Infectious cause	Mild-to-moderate symptoms, limiting instrumental ADLs	Monitor every 2–3 days
		Hypoxia	Lymphangitic spread	Medical intervention indicated	Grade 2: Hold ICPI ^{e,g}
		Increased oxygen requirements	Pulmonary embolism	Grade 3–4:	MPS 1–2 mg/kg/day
		Chest pain	Pleural effusion	Severe symptoms limiting self-care ADLs	Daily monitoring
		Radiographic changes	Consult:	New or worsening hypoxia	If imAE resolves to baseline, consider resuming treatment after steroid tapered over 4–6 weeks ^h
			Interventional pulmonology	Life-threatening urgent intervention indicated	Grade 3–4: Permanently discontinue ICPI
			Infectious disease		MPS 1–2 mg/kg/day increasing to 2–4 mg/kg/day if needed; taper as listed for Grade 2
			Diagnostics:		Refractory:
			CT scan		Consider additional immunosuppressant (eg, infliximab)
Renal			Bronchoscopy with biopsy		Grade 1: Continue ICPI
			PFTs		Hold all nephrotoxic drugs
	Interstitial nephritis	Often asymptomatic	Laboratory: serum creatinine, urinalysis	Grade 1:	Hydration
	Granulomatous nephritis	Increase in serum creatinine	Nephrology consult	Grade 2:	Grade 2–3: Hold ICPI ^{e,g,t}
	Glomerular lupus-like nephropathy	Vague nausea	Renal ultrasound	Creatinine 2.3 × above baseline	Monitor serum creatinine every 2–3 days
	Renal insufficiency	Emesis	Renal biopsy	Grade 3:	MPS 0.5–1.0 mg/kg/day; if no improvement increase to 1–2 mg/kg/day
	Renal failure	Decreased urine output		Creatinine >3 × baseline or >4.0 mg/dL	If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks ^h
		Cloudy/dark urine		Grade 4:	Grade 4: Permanently discontinue ICPI
		Blood in urine		Life-threatening	MPS 1–2 mg/kg/day with taper as listed for Grade 2–3
		Ankle swelling			Grade 1: Continue ICPI
Pancreatic			Laboratory: amylase and lipase levels, blood glucose	Grade 1:	Monitor laboratory results at least weekly
	Elevated amylase and lipase	May be asymptomatic	Pancreatic ultrasound	Lipase > ULN–1.5 × ULN	Grade 2–3: Hold ICPI ^{e,g,u}
	Pancreatitis	RUQ abdominal pain	CT scan	Grade 2:	MPS 0.5–1.0 mg/kg/day
	Type 1 diabetes mellitus	Nausea	Gastroenterology consult	Lipase 1.5–2 × ULN	If imAE resolves to Grade 1, consider resuming treatment after steroid tapered over 4–6 weeks ^f
		Vomiting	Endoscopy	Grade 3:	Grade 4: Permanently discontinue ICPI ^{v,w}
		Increase in stool frequency, bulk, or odor		>2–5 × ULN	MPS 1–2 mg/kg/day with taper as for Grade 2–3
		Statorrhea		Grade 4:	
				>5 × ULN	
					(Continued)

Table 3 (Continued)

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

(Continued)

Table 3 (Continued)

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

(Continued)

Table 3 (Continued)

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

HgI: life-threatening consequences;
urgent intervention indicated

Plt <25,000/mm³

Notes: ^aBased on published management algorithms^{23–27,38,39–97} and authors' clinical experience. ^bGrading 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. ^cFor Infanzi (durvalumab): hold ICPI if Grade 2 for >1 week. ^dFor 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. ^eFor 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. ^fFor 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. ^gFor Infanzi (durvalumab): 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. ^hPermanently discontinue Infanzi (durvalumab) for Grade 3 gastrointestinal imAE. ⁱPermanently discontinue Bavencio (avelumab) if Grade 3 imAE is recurrent. ^jFor Tecentriq (atezolizumab): resume treatment when imAE resolves to Grade 1 or less and is controlled with ≤10 mg/kg prednisone or equivalent per day. ^kKeytruda (pembrolizumab) may be continued in cases of Grade 2 hyperthyroidism and all-grade hypothyroidism. ^lFor Opdivo (nivolumab): no recommended dose modifications for hypothyroidism or hyperthyroidism. ^mFor Bavencio (avelumab): no recommended dose modifications for Grade 2 endocrinopathies. ⁿFor Tecentriq (atezolizumab): permanently discontinue for Grade 4 hypophysitis. ^oBegin taper if AE improves to Grade 2 for Opdivo (nivolumab) or if liver function tests improve for Yervoy (ipilimumab). ^pPermanently discontinue Infanzi (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. ^qPermanently discontinue Yervoy (ipilimumab), Keytruda (pembrolizumab), or Infanzi (durvalumab) for Grade 3 nephritis. ^rPermanently discontinue Yervoy (ipilimumab) for Grade 3 pancreatitis. Discontinue Keytruda (pembrolizumab) or Opdivo (nivolumab) if recurrent Grade 2 or 3. ^sFor 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. ^tHold Infanzi (durvalumab) if recurrent Grade 2 or 3. ^uFor grade 4 serum amylase or lipase elevation, hold Tecentriq (atezolizumab) and consider resuming treatment once imAE resolves to Grade ≤1. ^vPermanently discontinue Yervoy (ipilimumab) if Grade ≥2 or Grade 1 not responding to steroids within 2 weeks or requiring systemic therapy. ^wPermanently discontinue Opdivo (nivolumab), Keytruda (pembrolizumab), Tecentriq (atezolizumab), or Bavencio (avelumab) if Grade 3. ^xFor 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-Barré syndrome. ^yFor 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; HgI, 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.

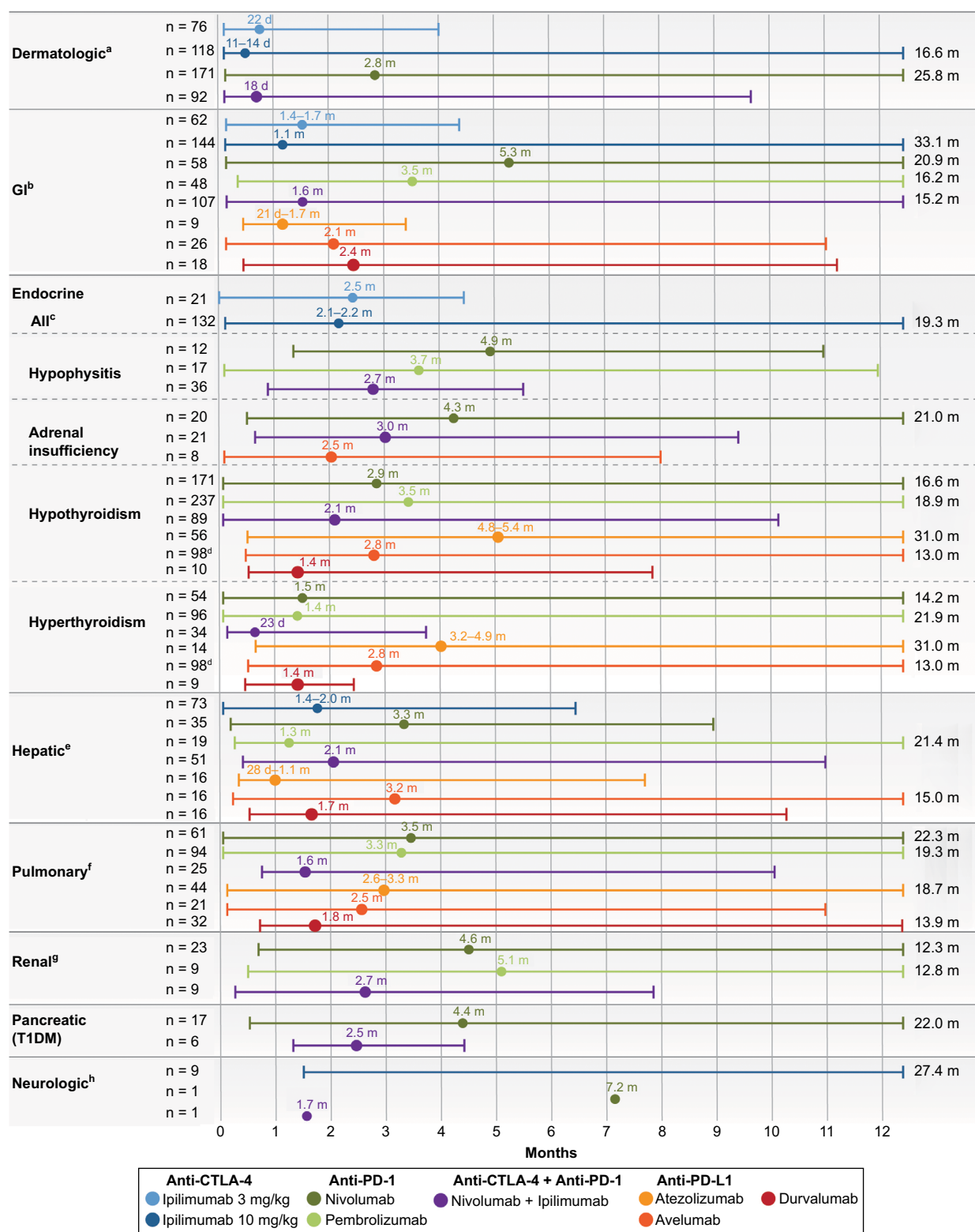


Figure 1 Time to onset of immune-mediated toxicities (median and range).^{22–27}

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). ^aDermatitis in ipilimumab studies; immune-mediated rash in nivolumab and nivolumab + ipilimumab studies. ^bEnterocolitis in ipilimumab studies; colitis in nivolumab, pembrolizumab, avelumab, and nivolumab + ipilimumab studies; colitis or diarrhea in atezolizumab and durvalumab studies. ^cIncludes hypopituitarism, adrenal insufficiency, hypothyroidism, hyperthyroidism, hypogonadism, thyroiditis, Cushing's syndrome, and Graves' ophthalmopathy. ^dHypothyroidism and hyperthyroidism are combined for avelumab. ^eHepatitis. ^fPneumonitis. ^gNephritis or renal dysfunction in nivolumab and nivolumab + ipilimumab studies; nephritis in pembrolizumab studies. ^hNeuropathy 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 ($\leq 4\%$) 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 ($\leq 1\%$, anti-PD-1 monotherapy [nivolumab]²³ or anti-PD-L1 monotherapy [atezolizumab,²⁵ avelumab,²⁶ durvalumab²⁷]; 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 $\leq 2\%$ 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%, durvalumab²⁷). 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, neurologic, 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 v4.0⁸⁸ 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 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 D₃ 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

Case 1: Rash	Case 2: Colitis	Case 3: Adrenal Insufficiency
68-year-old female presents 4 weeks after starting ICPI, with: • New-onset rash (initially on arms, treated with topical steroid cream) increased in distribution to chest, neck, scalp, back, and legs • Significant pruritus causing discomfort, lack of rest, and inability to carry out daily activities	54-year-old female presents 4 weeks after starting ICPI combination therapy^a with: • >6 diarrhea episodes per day • Abdominal cramping/pain and occasional incontinence of stool	63-year-old male presents 6 months after starting ICPI with: • Mild headache • Severe fatigue • Nausea (for 5 days)
Initial evaluation	Initial evaluation	Initial evaluation
• Physical examination – Maculopapular and maculopustular rash covering >30% body surface area • Dermatology consult • Skin biopsy	• Consider changes from baseline evaluations – 1 formed BM/day to 6+ loose stools; creatinine increase from 0.9 to 1.3 mg/dL • Rule out other potential causes (eg, infection) – Consider potential contacts with sick individuals; stool cultures to test for <i>Clostridium difficile</i> • Initiate supportive inpatient intervention (eg, hydration, bland diet, loperamide) • Request GI consult – Test for colitis with CT scan; if not definitive, proceed with colonoscopy	• Strongly consider endocrinopathy: evaluate for hypothyroidism and adrenal insufficiency by blood test
Diagnosis: Grade 3 rash; hold ICPI and initiate systemic and topical treatments	Diagnosis: Grade 3 colitis ^c ; hold ICPI and initiate systemic treatment	Diagnosis: adrenal insufficiency per laboratory results; hold ICPI
• Oral steroids (prednisone 60 mg/day), topical corticosteroid cream BID, and corticosteroid shampoo daily • Antibiotic prophylaxis and PPI while on oral prednisone • For pruritus, initiate oral antihistamines (diphenhydramine HCl or hydroxyzine HCl) or tricyclic antidepressant (doxepin HCl) • Reassess after 2 weeks – If rash worsens or remains Grade 3, consider hospitalization for IV corticosteroids; permanently discontinue ICPI – If rash improves, taper steroids over 4–6 weeks	• Methylprednisolone IV (1–2 mg/kg/day) • Antibiotic prophylaxis and PPI while on prednisone • If refractory, consider adding an additional immunomodulating agent (eg, infliximab IV)	• Initiate hormone repletion + oral prednisone (10 mg/BID) • Antibiotic prophylaxis and PPI while on oral prednisone • Request endocrine consult • If symptoms resolve within 1 week, taper prednisone to 10 mg/day after 2 weeks or per endocrinologist's recommendations
Once symptoms resolve to ≤ Grade 1, resume ICPI	Once symptoms resolve to ≤ Grade 1, switch to oral steroids (eg, prednisone 60 mg/day)	Once symptoms resolve to ≤ Grade 1, resume ICPI
• Maintain a physiologic dose of oral prednisone (5 mg/day) • Continue antibiotic prophylaxis and PPI while on prednisone	• Taper oral steroids slowly over 4–6 weeks – Observe patient for flare reaction during tapering • Continue antibiotic prophylaxis and PPI while on prednisone • Consider resuming ICPI combination therapy when symptoms resolve to baseline; in some cases, the decision may be to discontinue ipilimumab and treat with nivolumab monotherapy	• Explain “sick day rules” to patient (ie, need to increase prednisone when sick and then taper back to maintenance dose)

Figure 2 Sample imAE case management.^a

Notes: ^aCases based on fictitious patients. ^bIpilimumab + nivolumab. ^cPermanently 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 check-

lists (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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Disclosure

The authors report no conflicts of interest in this work.

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