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Immunotherapy toxicities: An SGO clinical practice statement

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HIGHLIGHTS

- Immune therapy is increasingly used in the treatment of gynecologic malignancies.
- Early recognition and appropriate management of immune-related toxicity is critical.
- Special considerations for immune therapy in gynecologic malignancies are reviewed.

1. Introduction

New insights into the role of the immune system in cancer evolution have ushered in a transformative era of immunotherapeutic drug development. Immune checkpoints are inhibitory pathways that facilitate self-tolerance and reduce unintended immune-mediated adverse events resulting from physiologic responses to pathogens [1]. These pathways, commonly controlled by ligand-receptor interactions on the surface of immune cells, have been identified as ideal targets for monoclonal antibodies to help enhance the body's immune response to cancer and overcome cancer-induced immune tolerance.

Since the initial United States Food and Drug Administration (FDA) approvals of pembrolizumab and nivolumab in 2014, immune checkpoint inhibitors (ICIs) have revolutionized the treatment of many solid tumors. In 2017, the FDA granted accelerated approval for pembrolizumab for the treatment of microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) recurrent cancers in a landmark disease site–agnostic manner. Since then, there have been four additional approvals for pembrolizumab and one for dostarlimab for the treatment of gynecologic cancers (Table 1).

To deliver these novel agents safely, a thorough understanding of their mechanisms of action and unique immune-related adverse events (irAEs) is required. Immune-mediated toxicity occurs when self-reactive T cells escape central tolerance as a consequence of immune checkpoint inhibition. The resultant toxicity can affect multiple organs, present with non-specific symptoms, and result in significant morbidity and even mortality if not identified and managed appropriately [1]. This review focuses on irAE management and special considerations for patients with gynecologic malignancies.

2. Basics of management

Clinicians and patients should be educated on the symptoms, signs, and potential risks of irAEs prior to the start of therapy and maintain a high level of suspicion during therapy. Suspected irAEs require prompt evaluation and treatment as clinically appropriate, including efforts to rule out other potential etiologies. While the management of irAEs must be tailored to the individual organ affected, several general principles can be applied [5]. Generalized principles of irAE grading and management are summarized in Table 2. In brief, for grade 1 irAEs, ICIs usually can be continued with close monitoring. Exceptions include certain neurologic, hematologic, and cardiac irAEs. Patients who develop any-grade myositis, myocarditis, or neurological symptoms should be referred to a specialist. For most grade 2 irAEs, ICIs usually are temporarily held until they resolve to grade ≤ 1, and in this setting, corticosteroids may be required. Oral corticosteroids are generally dosed at 1 mg/kg/day, but specific dosing considerations are available in Table 3. Grade 3 and 4 toxicities typically require the suspension of the ICI and initiation of high-dose intravenous corticosteroids, with planned tapering over at least 4–6 weeks; however, the irAE may flare up during steroid tapering. It is important to understand the short-term (e.g., opportunistic infections, gastritis) and long-term (e.g., diabetes, osteoporosis) adverse events associated with the use of moderate- to high-dose corticosteroids. Appropriate supportive medications, such as proton pump inhibitors and *Pneumocystis jirovecii* pneumonia prophylaxis may be required [5]. Apart from endocrinopathies that can be managed with hormone

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Table 1
Pivotal clinical trials resulting in FDA approval of ICIs in gynecologic cancer (and disease site–agnostic approvals).

Study	Disease Site	Treatment Arms	N	Primary Endpoint	Efficacy Outcome(s)	
Keynote studies[a] (Keynote 016, 164, 012, 028, and 158) [21–25]	Site agnostic, dMMR[b]	Pembrolizumab 10 mg/kg IV every 2 weeks or 200 mg IV every 3 weeks	*N* = 149 (MSI-H or dMMR) 59 CRC	ORR and DOR	ORR, 39.6% (95% CI: 31.7–47.9) ORR in non-CRC arm, 46%	CR, 7% PR, 32% Median DOR, not reached
Keynote 775 (NCT03517449) [26]	Endometrial cancer	Pembrolizumab + lenvatinib vs. Physicians' choice of chemotherapy: (doxorubicin or paclitaxel)	*N* = 827 (697 not dMMR)	BICR-assessed PFS and OS (co-primary endpoints)	Median OS, 17.4 vs 12 mo HR, 0.68 (95% CI: 0.56–0.84) *P* = 0.0001	Median PFS, 6.6 vs 3.8 mo HR, 0.60 (95% CI: 0.50–0.72) *P* < 0.0001
Keynote 158 (NCT02628067) [27]	Site agnostic, dMMR[b]	Pembrolizumab 200 mg IV every 3 weeks	*N* = 102 (all dMMR) (Approval based on 13 patients with high tumor mutational burden (≥10 mutations/ megabase)	ORR and DOR	ORR, 29% (95% CI: 21–39)	CR, 4% PR, 25% Median DOR, not reached
Keynote 158 (NCT02628067) [28]	Cervical cancer cohort	Pembrolizumab 200 mg IV every 3 weeks	*N* = 98 (Approval based on 77 patients with PD-L1 CPS ≥1)	ORR and DOR	ORR, 14.3% (95% CI: 7.4–24.1)	CR, 2.6% PR, 11.7% Median DOR, not reached
GARNET Trial (NCT02715284) Cohort A1 [29]	Endometrial cancer	Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks	*N* = 71 (all dMMR)	ORR and DOR	ORR, 42.3% (95% CI: 30.6–54.6)	CR, 12.7% PR, 29.6% Median DOR: Not reached
GARNET Trial (NCT02715284) [30]	Site agnostic, dMMR	Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks	*N* = 209 (all dMMR)	ORR and DOR	ORR, 41.6% (95% CI: 34.9–48.6)	CR, 9.1% PR, 32.5% Median DOR, 34.7 months
Keynote 826 (NCT03635567) [31]	Cervical cancer, PD-L1+	Pembrolizumab 200 mg IV every 3 weeks with platinum/paclitaxel +/−bevacizumab vs platinum/paclitaxel +/−bevacizumab	*N* = 617	BICR-assessed PFS and OS	Median PFS, 10.4 vs 8.4 mo HR, 0.62 (95% CI: 0.5–0.77) *P* = 0.001	Median OS, Not reached vs 16.3 mo HR, 0.64 (95% CI: 0.5–0.81) P = 0.001

ICI = immune checkpoint inhibitor; mo = months; HR = hazard ratio; dMMR = mismatch repair deficient; N = number of patients enrolled; ORR = objective response rate; CRC = colorectal cancer; CR = complete response; PR = partial response; DOR = duration of response, BICR = blinded independent central review; OS = overall survival; PFS = progression-free survival; PD-L1 = programmed death ligand 1; CPS = combined positive score.
[a] (Keynote 016 [NCT 01876511], Keynote 164 [NCT 02460198], Keynote 012 [NCT 01848834], Keynote 028 [NCT 02054806], and Keynote 158 [NCT 02628067]).
[b] Included endometrial, ovarian, cervical, vaginal, and vulvar cancer.

replacement, grade 4 irAEs typically require permanent discontinuation of the ICI. Many irAEs require consultation with a specialist. Refractory cases may necessitate hospitalization and additional immunomodulatory agents, such as infliximab. Most reported fatal irAEs occur within the first 1–2 months of ICI initiation [1,2]. IrAEs can occasionally occur even months after ICI discontinuation.

3. Management of common toxicities

The most common irAEs of ICI therapy are organized by usual timing of onset and frequency (Fig. 1). A summary of the grading of specific irAEs can be found in Table 4. The organ-specific management strategies of the more common irAEs are detailed in Table 3.

3.1. Dermatologic toxicity

Dermatologic toxicities, which are among the most common irAEs, occur in 10–50% of patients on ICI therapy [1,3,4]. The incidence varies by agent; cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitors are associated with the highest rate (up to 50%), followed by programmed cell death protein 1 (PD-1) inhibitors (30–40%). Programmed death ligand 1 (PD-L1) inhibitors have the lowest rate of dermatologic toxicity, affecting less than 10% of patients [5]. The median onset of a dermatologic toxicity is 3 weeks [6]. Most dermatologic irAEs are grade 1 or 2, and are often successfully managed with topical agents, ***not*** necessitating ICI interruption [4,5].

Table 2
Generalized immune-related adverse event grading and management.

Definition	Management
Grade 1:	
Mild, asymptomatic or mild symptoms only, intervention not indicated	Continue ICI with close monitoring[a] Supportive care
Grade 2:	
Moderate symptoms Respond rapidly to intervention	Consider holding ICI until grade ≤ 1 Consider systemic treatment with steroids Supportive care
Grade 3:	
Severe or medically significant but not immediately life-threatening Not rapidly responsive to supportive treatment	Hold ICI with consideration of permanent discontinuation pending clinical scenario Initiate high-dose intravenous corticosteroids with tapering over at least 4–6 weeks
Hospitalization or prolonged hospitalization indicated	Hospitalization and specialist consultation Supportive treatment
Grade 4:	
Life-threatening consequences Urgent intervention indicated	Permanent discontinuation of ICI Intensive Care

[a] Exceptions include certain neurologic, hematologic, and cardiac irAEs which may warrant permanent discontinuation of the ICI.

Table 3
Basics of management for immune-related adverse events by grade.

Toxicity	Diagnostic Work-up	Check Point Inhibition	Immunosuppression	Supportive Care
Gastrointestinal				
Colitis				
G1	Rule out infection: stool culture, ova, parasites, *Clostridium difficile*; inflammatory markers	Continue	None	Symptomatic treatment: • Loperamide • Atropine sulfate • Budesonide if symptoms persist beyond 2–3 days • Dietary modification
G2	Rule out infection; inflammatory markers; **GI consult;** colonoscopy may be beneficial	Hold; resume if symptoms improve to grade ≤ 1 or when prednisone is tapered to <10 mg daily	• If diarrhea only, observe for 2–3 days; if no improvement, start **oral prednisone 1 mg/kg/day** • If diarrhea and colitis, start **oral prednisone 1 mg/kg/day**; if no improvement after 48 h, increase to **oral prednisone 2 mg/kg/day** • Taper over 4–6 weeks if symptoms improve; can taper to moderate doses over several days, followed by a slower weeks-long taper • If no improvement after 3 days, start **infliximab 5 mg/kg q 2 weeks or vedolizumab 300 mg per GI consult**[a]	Symptomatic treatment: • Loperamide • Atropine sulfate • Budesonide if symptoms persist beyond 2–3 days • Dietary modification
G3	Rule out infection; inflammatory markers; **GI consult**; colonoscopy may be beneficial	Hold; resume if symptoms improve to grade ≤ 1 or when prednisone is tapered to <10 mg daily	• **IV prednisone 1 mg/kg/day**; if no improvement after 48 h, increase to **IV prednisone 2 mg/kg/day** • Taper over 4–6 weeks if symptoms improve; can taper to moderate doses over several days, followed by a slower weeks-long taper • If no improvement after 48 h, start i**nfliximab or vedolizumab** • **Consider microbiota transfer**	Consider hospitalization
G4	Rule out infection; inflammatory markers; **GI consult**; colonoscopy may be beneficial	Discontinue Checkpoint inhibition should also be discontinued if symptoms return to grade 3/4 upon resumption	• **IV prednisone 1 mg/kg/day**; if no improvement after 48 h, increase to **IV prednisone 2 mg/kg/day** • Taper over 4–6 weeks if symptoms improve; can taper to moderate doses over several days, followed by a slower weeks-long taper • If no improvement after 48 h, start i**nfliximab or vedolizumab** • **Consider microbiota transfer**	Hospitalization
Hepatitis				
G1	Rule out viral, drug-induced, or autoimmune causes; monitor LFTs several times per week until resolution, then weekly	Continue	None	
G2	Rule out viral, drug-induced, or autoimmune causes; **GI consult**; monitor LFTs daily until resolution, then weekly	Hold; resume if symptoms improve to grade ≤ 1	• Oral **prednisone 0.5-1 mg/kg/day** • Taper over 4–6 weeks if symptoms improve; can taper to moderate doses over several days, followed by a slower weeks-long taper • Consider alternative immunosuppressive agent if no improvement after 48 h: **mycophenolate mofetil 500 mg BID** or **tacrolimus 0.10–0.15 mg/kg/daily** (trough 5-20 ng/mL) **Infliximab is CONTRAINDICATED due to potential hepatotoxicity**	
G3/G4	Rule out viral, drug-induced, or autoimmune causes; **GI consult**; monitor LFTs daily until resolution, then weekly	Discontinue	• **IV prednisone 1 mg/kg/day**; if no improvement after 48 h, increase to **IV prednisone 2 mg/kg/day** • Consider alternative immunosuppressive agent if no improvement after 48 h: **mycophenolate mofetil 500 mg BID** or **tacrolimus 0.10–0.15 mg/kg/daily** (trough 5-20 ng/mL) **Infliximab is CONTRAINDICATED due to potential hepatotoxicity**	Hospitalization
Dermatologic				
G1	Mucocutaneous examination	Continue	Topical corticosteroids For body: • **Clobetasol propionate 0.05% BID** • **Halobetasol propionate 0.05% BID** • **Betametasone diproprionate 0.05% BID**	Oral antihistamines • **Cetirizine/loratadine 10 mg** • **Hydroxyzine 10–25 mg QID**

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Table 3 (*continued*)

Toxicity	Diagnostic Work-up	Check Point Inhibition	Immunosuppression	Supportive Care
			For face: • **Alclometasone 0.05% BID/TID** • **Desonide 0.05% BID/TID** • **Hydrocortisone 2.5% BID**	
G2	Mucocutaneous examination; LFTs; KFTs; serum tryptase and IgE levels; non-urgent **dermatology consult**	Hold; resume if symptoms improve to grade ≤ 1	Topical corticosteroids For body: • **Clobetasol propionate 0.05% BID** • **Halobetasol propionate 0.05% BID** • **Betametasone diproprionate 0.05% BID**	Oral antihistamines: • **Cetirizine/loratadine 10 mg** • **Hydroxyzine 10-25 mg QID**
G3/G4	Mucocutaneous examination; LFTs; KFTs; serum tryptase and IgE levels; urgent **dermatology consult**; skin biopsy	Hold; resume if symptoms improve to grade ≤ 1	For face: • **Alclometasone 0.05% BID/TID** • **Desonide 0.05% BID/TID** • **Hydrocortisone 2.5% BID** • Start oral **prednisone 0.5–1 mg/kg/day** until symptoms resolve to grade < 1 • Taper over 4 weeks • Start **oral prednisone 1 mg/kg/day** until symptoms resolve to grade ≤ 1 • Taper over 4 weeks • If no improvement after 48 h, increase to **oral prednisone 2 mg/kg/day**	Oral antihistamines • **Cetirizine/loratadine 10 mg** • **Hydroxyzine 10–25 mg QID** • **Gabapentin** or **pregabalin 100–300 mg TID** for severe pruritis
Endocrine				
LH/FSH/testosterone, prolactin, TSH, FT4, ACTH (AM), cortisol (AM). MRI brain with pituitary cuts and visual field testing. **CONSULT ENDOCRINE** (work-up is essentially the same for all endocrinopathies. It is important to rule out central adrenal insufficiency.				
Hypothyroid				
G1		Continue	None	
G2		Continue	None	Thyroid replacement: • **1.6 μg/kg** in young/healthy patients • Reduced dose **25–50 μg** in elderly patients/cardiovascular disease • Repeat TSH and FT4 after 6–8 weeks accordingly • If TSH is above reference range, increased by 12.5–25 μg
G3/G4		Hold until work-up is completed and appropriate hormone replacement is started Can be resumed after resolution of symptoms to grade ≤ 2	None	Thyroid replacement: • **1.6 μg/kg** in young/healthy patients • Reduced dose **25–50 μg** in elderly patients/cardiovascular disease • Repeat TSH and FT4 after 6–8 weeks accordingly • If TSH is above reference range, increased by 12.5–25 μg
Hyperthyroid				
G1		Continue	None	
G2	For persistent hyperthyroidism (>6 weeks), work-up for Graves' disease (TSI or TRAb) and management per endocrine consult	Continue	None	Hyperthyroid phase: Symptomatic management • Beta blockers for tachycardia: **propranolol 20–40 mg 4× daily (240–480 mg daily)** or **atenolol 25–50 mg daily** (titrate for HR < 90) Hypothyroid phase: the hyperthyroid phase will typically evolve into a hypothyroid phase. Manage as above.
G3	For persistent hyperthyroidism (>6 weeks), work-up for Graves Dx (TSI or TRAb) and management per endocrine consult	Hold until work up is completed and the patient is no longer symptomatic	High-dose corticosteroids are not routinely required. If severe symptoms or concern for thyroid storm, **prednisone 1-2 mg/kg/day** tapered over 1–2 weeks.	Hyperthyroid phase: symptomatic management. • Beta blockers for tachycardia: **propranolol 20-40 mg 4× daily (240–480 mg daily)** or **atenolol 25-50 mg daily** (titrate for HR < 90).

Table 3 (*continued*)

Toxicity	Diagnostic Work-up	Check Point Inhibition	Immunosuppression	Supportive Care
G4	For persistent hyperthyroidism (> 6 weeks) work-up for Graves' disease (TSI or TRAb) and management per endocrine consult	Hold until work-up is completed and the patient is no longer symptomatic	If severe symptoms or concern for thyroid storm, **prednisone 1–2 mg/kg/day** tapered over 1–2 weeks.	Hypothyroid phase: the hyperthyroid phase will typically evolve to a hypothyroid phase. Manage as above. Hyperthyroid phase: Symptomatic management. • Beta blockers for tachycardia: **propranolol 20–40 mg 4× daily (240–480 mg daily)** or **atenolol 25–50 mg daily** (titrate for HR < 90).
Hypophysitis				Hypothyroid phase: the hyperthyroid phase will typically evolve into a hypothyroid phase. Manage as above.
G1		Continue	None	
G2/G3		Hold until work-up is completed and appropriate hormone replacement is started	• If central adrenal insufficiency, start physiologic steroid replacement: **Hydrocortisone 10–20 mg PO q AM and 5-10 mg PO q afternoon**. • If hypothyroid, treat as above. **Start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis**	
G4		Discontinue	• If central adrenal insufficiency, start physiologic steroid replacement: **Hydrocortisone 10–20 mg PO q AM and 5-10 mg PO q afternoon**. • If hypothyroid, treat as above. **Start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis.** • Consider initial pulse dose therapy with **prednisone 1–2 mg/kg PO** daily tapered over 4–6 weeks.	
Primary Adrenal Insufficiency				
G1		Continue	• **Hydrocortisone 10–20 mg PO q AM and 5–10 mg PO q afternoon** • May require **fludrocortisone (0.1 mg/day)** for mineralocorticoid replacement • Titrate dose up or down as symptoms dictate.	
G2		Continue	Stress dose steroids: • **Hydrocortisone 20–30 mg PO q AM and 10–20 mg PO q afternoon.** • Taper down to maintenance doses (**Hydrocortisone 10–20 mg PO q AM and 5-10 mg PO q afternoon)** over 5–10 days.	
G3/4		Hold; resume when steroids are tapered to maintenance dose	• IV hydration: **normal saline 2 L.** • IV steroids: **hydrocortisone 100 mg or dexamethasone 4 mg** on arrival. • Followed by stress dose steroids: **Hydrocortisone 20–30 mg PO q AM and 10–20 mg PO q afternoon.** • Taper down to maintenance doses (**Hydrocortisone 10–20 mg PO q AM and 5–10 mg PO q afternoon**) over 5–10 days.	Hospitalization
Pulmonary				
Pneumonitis				
G1	Oxygen saturation, Chest CT, pulmonary function tests, and **pulmonary consultation**	Hold ICI until improved	None	• Reimage with each cycle • If symptoms progress treat as higher grade • Self-monitoring of symptoms and oxygen saturation
G2	Same as above, plus bronchoscopy with bronchoalveolar lavage and possible biopsies	Hold ICI; resume re-challenge if imaging and symptoms resolve and steroids are tapered	• **IV steroids** prednisone 1 mg/kg/day (or oral equivalent). • Taper over 4 weeks once symptoms improve. • **If symptoms do not improve or worsen treat as grade 3–4.**	• Consider hospitalization • Consult pulmonary and infectious disease • Reimage with each cycle

(*continued on next page*)

Table 3 (*continued*)

Toxicity	Diagnostic Work-up	Check Point Inhibition	Immunosuppression	Supportive Care
G3/4	As above	Permanently discontinue	IV steroids: Prednisone 1 mg/kg/day or equivalent with slow taper.	• Self-monitoring of symptoms and oxygen saturation • Hospitalization • Consult pulmonary and infectious disease • Consider ICU care • Permanently discontinue ICI

GI = gastrointestinal; LFT = liver function test; KFT = kidney function test; IgE = immunoglobulin E; LH = luteinizing hormone; FSH = follicle-stimulating hormone; TSH = thyroid-stimulating hormone; FT4 = free thyroxine; ACTH = adenocorticotropic hormone; MRI = magnetic resonance imaging; TSI = thyroid-stimulating immunoglobulin; TRAb = thyrotropin receptor antibody.

[a] Tuberculosis and hepatitis testing must be performed prior to initiating infliximab.

The most common skin finding is a non-specific, maculopapular rash often associated with pruritis. Other dermatologic manifestations include lichenoid reactions, psoriasis, acneiform rashes, vitiligo-like lesions, autoimmune skin disease, sarcoidosis, or nail and oral mucosal changes. Although rare, severe cutaneous adverse reactions (SCARs) can occur and include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS is a serious multiorgan disease characterized by rash, fever, lymphadenopathy, leukocytosis with eosinophilia and atypical lymphocytes, and liver dysfunction.

Evaluation of any dermatologic irAE should include a full history and assessment of all skin surfaces and mucous membranes with documentation of the type of lesion/rash and extent by percent of body surface area (BSA). Consider clinical photography prior to initiating treatment. Same-day referral to dermatology is indicated for grade 3–4 toxicity, blisters covering >10% BSA, rash with mucosal involvement, rash covering >30% BSA, and/or painful rash. Non-urgent referral is appropriate for rashes with unclear diagnosis, worsening grade 2 rash, and all rashes not responsive to topical steroids. Pruritus may improve with oral antipruritics and pregabalin or gabapentin. Patients who develop SCARs require immediate hospitalization, dermatology consultation, and systemic immunosuppression. An overlap in the spectrum of skin toxicities observed when ICIs are given in combination with targeted agents, such as lenvatinib, can make it challenging to identify the causative agent. A generalized maculopapular rash and pruritis are common manifestations of ICI-related cutaneous toxicity, whereas lenvatinib tends to be more frequently associated with hand foot syndrome, mucositis, and xerosis. Due to its short half-life, a brief dose interruption of lenvatinib may help clarify the causative agent.

3.2. Gastrointestinal toxicity

Gastrointestinal (GI) toxicities, including diarrhea, colitis, and hepatitis, are also among the most common irAEs with ICI therapy. Low-grade nausea is relatively common. Mild, self-limited diarrhea can occur at the initiation of therapy and is distinct from immune-mediated colitis. Diarrhea-associated abdominal pain, mucus/blood in the stool, and fever should prompt immediate concern for immune-related colitis, which can be life-threatening.

The incidence of diarrhea ranges from 20% with single-agent ICI therapy to 44% with combination therapy [7]. The incidence of colitis

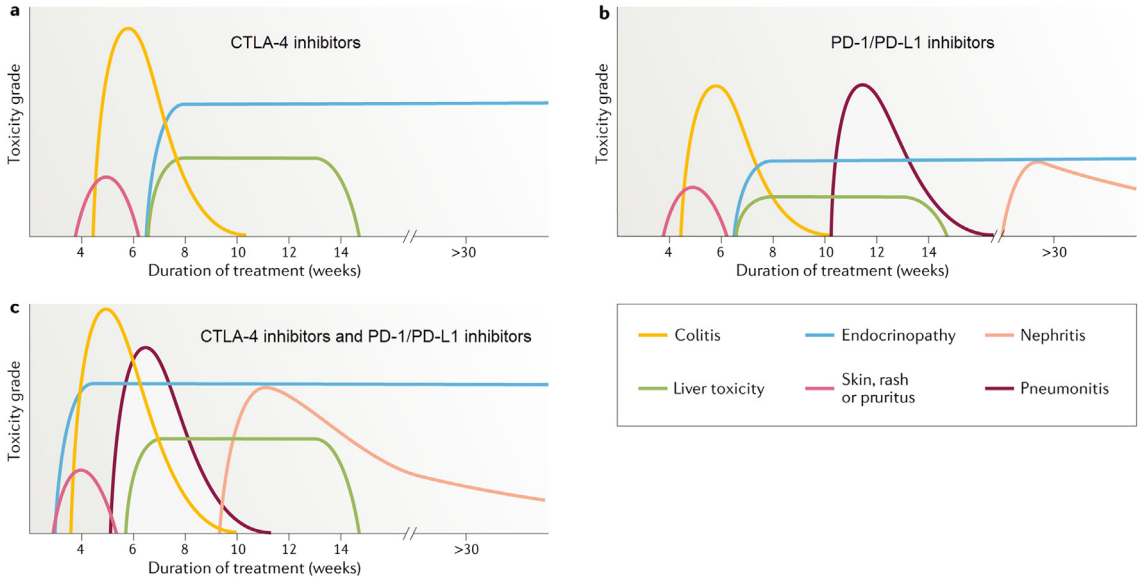

Fig. 1. Median time to onset of immune-related adverse events (irAEs)

a) Onset of irAEs with CTLA-4 inhibitors
b) Onset of irAEs with PD-1/PD-L1 inhibitors
c) Onset of irAEs with combined CTLA-4 and PD-1/PD-L1 inhibitors
d) Reprinted with permission from RightsLink: Martins, F., et al., Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev. Clin Oncol, 2019. 16(9): p. 563–580.

Table 4
Grading of immune-related adverse events (CTCAE v5).

Organ System	Grading
Dermatologic	Maculopapular rash 1: Macules/papules covering <10% BSA +/− pruritis, burning, tightness 2: Macules/papules covering 10–30% of BSA, limiting ADL and requiring intervention 3: Macules/papules covering >30% BSA and impacting self-care ADL 4: n/a Pruritis 1: Mild or localized 2: Intense or widespread, intermittent, skin changes from scratching 3: Intense or widespread, constant, and impacting self-care ADL 4: n/a Bullous skin lesions 1: Asymptomatic, blisters <10% BSA, no erythema 2: Symptomatic, blisters requiring intervention due to QOL impact, covering 10–30% BSA 3: Blisters covering >30% BSA, with pain and limiting ADL (symptomatic) 4: Blisters covering >30% BSA, with associated fluid or electrolyte disturbances (symptomatic) Serious cutaneous adverse reactions (SCARs) 1: n/a 2: Maculopapular rash covering 10–30% BSA, with systemic symptoms, lymphadenopathy, or facial swelling 3: Skin sloughing of <10% BSA, with mucosal involvement–associated signs (erythema, purpura, epidermal attachment, mucous membrane detachment) 4: Skin erythema and blistering/sloughing covering >10% BSA, with associated signs (erythema, purpura, epidermal attachment, mucous membrane detachment) and/or systemic symptoms with associated lab abnormalities in the setting of DRESS/DIHS
Gastrointestinal	Diarrhea/Colitis 1: Asymptomatic, <4 stools per day over baseline 2: Abdominal pain, mucus or blood in stool, diarrhea 4–6 times per day over baseline 3: Severe abdominal pain, change in bowel habits, peritoneal signs, diarrhea 7 times or more per day over baseline 4: Life threatening Hepatitis 1: AST, ALT >ULN to 3× ULN, total bilirubin >ULN to 1.5× ULN 2: AST, ALT >3× to 5× ULN, total bilirubin 1.5× to 3× ULN 3: AST/ALT >5× ULN, total bilirubin >3× ULN 4: AST/ALT >5× ULN, total bilirubin >3× ULN; or AST/ALT >20× ULN,
Endocrine	Hypophysitis 1: Asymptomatic, diagnostic observation, intervention not warranted 2: Moderate, minimal/non-invasive intervention needed; limiting instrumental ADL 3: Severe, hospitalization required; limiting self-care ADL 4: Life threatening; urgent intervention indicated Hypothyroid 1: Asymptomatic, diagnostic observation, intervention not warranted 2: Symptomatic, thyroid replacement needed; limiting instrumental ADL 3: Severe, hospitalization indicated; limiting self-care ADL 4: Life threatening; urgent intervention indicated Hyperthyroid 1: Asymptomatic, diagnostic observation, intervention not warranted 2: Symptomatic, thyroid suppression needed; limiting instrumental ADL 3: Severe, hospitalization indicated; limiting self-care ADL 4: Life threatening; urgent intervention indicated Hyperglycemia 1: Abnormal glucose above baseline with no medical intervention 2: Change in daily management from baseline for diabetic, oral antiglycemic agent 3: Insulin therapy; hospitalization indicated 4: Life threatening; urgent intervention indicated
Pulmonary	Pneumonitis 1: Asymptomatic; diagnostic observation 2: Symptomatic, limiting instrumental ADL; medical intervention indicated 3: Severe symptoms, limiting self-care ADL; oxygen indicated 4: Life-threatening respiratory compromise; urgent intervention indicated Sarcoidosis (no grading available) 1: n/a 2: Managed based on standard or care
Rheumatologic	Inflammatory Arthritis 1: Mild pain with inflammatory symptoms, erythema, or joint swelling 2: Moderate pain with inflammatory symptoms, erythema, or joint swelling; limiting instrumental ADL 3: Severe pain with inflammatory symptoms, erythema or joint swelling, erosion or irreversible joint damage; limiting self-care ADL 4: n/a
Renal	Nephritis 1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5-2× baseline 2: Creatinine 2-3× baseline 3: Creatinine >3× baseline or > 4.0 mg/dL; hospitalization indicated 4: Life threatening; dialysis indicated
Neurologic	Encephalopathy/Leukoencephalopathy/PRES 1: Mild symptoms 2: Moderate symptoms; limiting instrumental ADL 3: Severe symptoms; limiting self-care ADL 4: Life threatening; urgent intervention indicated Peripheral motor and sensory neuropathy 1: Mild symptoms 2: Moderate symptoms; limiting instrumental ADL 3: Severe symptom; limiting self-care ADL 4: Life threatening; urgent intervention indicated
Hematologic	Anemia 1: Hemoglobin lower limit of normal to 10 g/dL 2: Hemoglobin <10 to 8 g/dL 3: Hemoglobin <8 g/dL; transfusion indicated 4: Life-threatening anemia; urgent intervention indicated Thrombocytopenia 1: Platelets lower limit of normal to 75 K 2: Platelets <75 K to 50 K 3: Platelets <50 K to 25 K 4: Platelets <25 K
Cardiovascular	Myocarditis 1: n/a 2: Symptoms with moderate activity or exertion 3: Moderately abnormal testing or symptoms with mild activity 4: Moderate to severe decompensation; IV meds or interventions required; life threatening
Ocular	Uveitis 1: Asymptomatic; diagnostic observation 2: Symptomatic, limiting instrumental ADL, moderate decrease in visual acuity (20/40 or better) 3: Symptomatic, limiting self-care ADL, marked decrease in visual acuity (worse than 20/40) 4: Blindness in the affected eye (20/200 or worse)

BSA = body surface area; ADL = activities of daily living; QOL = quality of life; SCARs = severe cutaneous adverse reactions; DRESS = drug reaction with eosinophilia and systemic symptoms; DIHS = drug-induced hypersensitivity syndrome; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; PRES = posterior reversible encephalopathy syndrome.

is 8–22% with CTLA-4 inhibitors; the rates of colitis are much lower with single-agent anti–PD-1 and anti–PD-L1 ICI therapy [1]. CTLA-4 inhibitor combination therapy is associated with more severe colitis. The average onset to immune-related colitis/diarrhea is 9 weeks from initiation of therapy but can present after the first infusion [8,9]. Diarrhea and colitis can recur months after discontinuation of immunotherapy, with continued flare-ups over time, similar to inflammatory bowel disease [10].

The evaluation of diarrhea or abdominal pain includes a history and physical exam. Infectious etiologies should be excluded (e.g., *Clostridium difficile*, cytomegalovirus [CMV], and ova/parasites). Agents administered in combination with ICI, such as lenvatinib, may also cause diarrhea. Lenvatinib-associated diarrhea tends to have an earlier onset, often occurring during the initial 1–2 cycles of therapy, whereas immune-related diarrhea is more often seen in cycle 3. Lenvatinib may cause low volume, frequent bowel movements (3–5 times/day) whereas large volume, loose, watery stool with associated pain, mucus or bleeding is more concerning for immune-mediated diarrhea.

Grade 2 or higher immune-related diarrhea warrants prompt initiation of systemic treatment and referral to gastroenterology for endoscopy. Infliximab or vedolizumab therapy are used if there is no response to steroids within 3–5 days [9,11]. Refractory cases may benefit from microbiota transfer. Colonoscopy is the most accurate way to determine the extent of colitis, but cross-sectional imaging can identify wall thickening, mesenteric engorgement, and peri-colonic fat stranding, which often occur with immune-related colitis [9,12]. Pancolitis or focal colitis involving a segment of the colon can occur. Routine mucosal biopsies are recommended because significant histologic inflammation can occur despite normal-appearing mucosa on colonoscopy, and to exclude CMV infection [9]. If intestinal perforation is suspected, a surgeon who is experienced in abdominal surgery should be immediately consulted.

Hepatitis is a less common GI irAE with ICI therapy. Liver enzymes should be evaluated prior to each ICI cycle. The incidence of hepatitis is 1–2% with anti–PD-1/anti–PD-L1 therapy but can reach up to 30% with combination CTLA-4 blockade [13]. Onset generally occurs within 6–14 weeks after ICI initiation [13]. Hepatitis is generally asymptomatic but can present with fever. It is characterized by the elevation of transaminases with or without hyperbilirubinemia. If transaminitis develops, creatine kinase (CK) should be checked to evaluate for myositis and myocarditis as an alternative etiology. Other causes of liver damage, such as viral infection, cancer progression, drug injury, or alcohol use, should be excluded, as well as thromboembolic events and outflow obstruction. Most cases resolve with discontinuation of therapy, but severe acute liver injury has been reported. In cases of steroid-refractory immune hepatitis, mycophenolate mofetil is used. Infliximab can cause further liver injury and is contraindicated.

3.3. Endocrine toxicity

The most common endocrine irAEs with ICI therapy are related to thyroid dysfunction (hypothyroidism and thyroiditis) and hypopituitarism/hypophysitis (central hypothyroidism, central adrenal insufficiency, and hypogonadotropic hypogonadism). Other, rarer endocrine irAEs include primary adrenal insufficiency, hypercalcemia, hypoparathyroidism and pancreatitis. Amylase and lipase may be elevated at baseline in patients with advanced gynecologic cancers, so patients should be assessed for signs or symptoms of pancreatitis. Additional imaging is warranted if pancreatitis is suspected. ICI does not need to be held or discontinued for isolated laboratory elevations in the absence of clinical symptoms or signs suggestive of pancreatitis. Type 1 diabetes mellitus, although rare, may present acutely with diabetic ketoacidosis and usually requires life-long insulin. Most endocrine irAEs persist even after treatment of the irAE.

Primary thyroid dysfunction occurs in 6–20% of patients [9]. Patients with symptoms of thyroid dysfunction or labs indicating primary hypothyroidism (elevated thyroid stimulating hormone [TSH] and low free thyroxine [FT4]) levels should be evaluated. Thyroid antibodies, including thyroid peroxidase (TPO), can be tested. Thyroid replacement should be initiated, with repeat testing in 6–8 weeks. A maintenance dose is identified when TSH normalization is achieved.

Immune-related thyrotoxicosis (elevated FT4 with low or normal TSH levels) is most commonly caused by thyroiditis, but in rare cases by Graves' disease. Thyroiditis is most common with PD-1/PD-L1 inhibition, whereas Graves' disease is more common with CTLA-4 inhibition. Thyrotoxicosis generally presents approximately 1 month after the initiation of ICI therapy, with subsequent development of permanent hypothyroidism. No treatment is necessary during the thyrotoxic phase, although cardio-selective beta blockade can be used in symptomatic patients. TPO, thyroid-stimulating immunoglobulin, and thyroid receptor antibody can be evaluated for Graves' disease. Thyroid function tests should be performed every 2–3 weeks during the thyrotoxic phase, and thyroid replacement should be initiated once the hypothyroid phase begins.

Hypophysitis is an uncommon but serious irAE associated with ICI therapy that can present with non-specific symptoms and progress to secondary adrenal insufficiency, hypothyroidism, and hypogonadism. It occurs more often with CTLA-4 inhibition and typically manifests within 8–10 weeks [7]. Hypophysitis most commonly presents with headache (85%) or fatigue (66%) or can be identified by low TSH and FT4 levels, suggesting central hypothyroidism. A strong clinical suspicion must be maintained for a complaint of headache, fatigue, anorexia, and/or nausea. Thyroid function and glucose tests are performed at baseline and monitored routinely [9]. Patients with symptoms concerning for hypophysitis should undergo morning serum testing for thyroid function, adrenal function (adrenocorticotropic hormone [ACTH] and cortisol), and if appropriate, gonadal hormones (follicle stimulating hormone/luteinizing hormone/estradiol), as well as magnetic resonance imaging (MRI) of the pituitary sella. MRI signs of pituitary enlargement may precede biochemical laboratory changes. Steroids should not be administered until the diagnostic work-up has been initiated [9].

3.4. Pulmonary toxicity

Pneumonitis, the most common pulmonary irAE associated with ICI therapy, occurs in approximately 5% of patients but accounts for 35% of irAE-associated fatalities with PD-1/PD-L1 inhibition [2]. Other rare pulmonary adverse events include pleural effusions, sarcoidosis, and sarcoid-like granulomatous disease. Pneumonitis presentation can vary, and up to 33% of patients are asymptomatic and diagnosed on routine imaging [9,14]. New respiratory symptoms, such as shortness of breath, cough, chest pain, fatigue or wheezing, warrants prompt evaluation for pneumonitis. Median onset of pneumonitis is 10 weeks [14], but it can present over a year after ICI initiation. Up to 50% of patients have a concomitant irAE [9].

Grade 1–2 toxicity can be managed in an outpatient setting. Patients who develop grade 1 toxicity may be re-challenged following resolution of infiltrates on CT. Grade 2 or higher toxicity is treated with systemic steroids, with slow tapering (4–6 weeks), as rapid tapering has been associated with recurrence. *Re*-challenge following grade 2 toxicity may be considered with resolution of symptoms and close pulmonary follow up. Grade 3 toxicity should not be re-challenged.

Oxygen saturation, chest computed tomography (CT), pulmonary function tests, and in some cases, a 6-min walk test and pulmonary consultation are appropriate for new pulmonary complaints. CT is superior to plain films for identifying pneumonitis. Four distinct patterns of pneumonitis have been described (organizing pneumonia pattern, non-specific interstitial pneumonia pattern, hypersensitivity pneumonitis, and diffuse alveolar damage). Radiologic findings usually include ground-glass opacities and reticular markings with traction bronchiectasis (non-specific interstitial pneumonia pattern) or patchy areas of consolidation or ground-glass opacities often seen along the lung periphery (organizing pneumonia pattern). Bronchoscopy should be considered for new or persistent infiltrates to help with a differential diagnosis that includes both infection and ICI toxicity. ICI-mediated infiltrates are typically bilateral but can be asymmetric. Pulmonary and infectious diseases consults should be obtained. Clinical and radiological findings can mimic pneumonia; therefore, broad-spectrum antibiotics as well as systemic steroids are recommended in symptomatic patients, because a delayed diagnosis may compromise a patient's clinical

outcome and is particularly challenging in the setting of pre-existing lung disease.

3.5. Rheumatologic/musculoskeletal toxicity

Reports of rheumatologic irAEs range from 1% to 43% for arthralgia and 2% to 20% for myalgia [15]. Rheumatologic irAEs may present as seronegative spondyloarthropathy, polyarthritis of the small joints of the hands, similar to rheumatoid arthritis, or large joint arthritis combined with uveitis and conjunctivitis. Other rheumatologic irAEs include myositis, sicca syndrome, giant cell arteritis, polymyalgia rheumatica, systemic lupus erythematosus, vasculitis, and sarcoidosis. Almost a third of patients with myositis also experience myocarditis.

Acute musculoskeletal complaints during or after ICI therapy may represent rheumatologic irAEs, that if left untreated, could lead to joint erosion and irreversible damage. Musculoskeletal symptoms may continue despite ICI therapy discontinuation. Rheumatologic irAEs may impact a patient's quality of life considerably, with loss of ability to perform instrumental activities of daily living. Grade 2 symptoms are treated with systemic steroids and prompt rheumatology referral. Early joint erosion may occur despite steroid administration. Disease-modifying anti-rheumatic drugs (DMARDs), such as tumor necrosis factor inhibitors, methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine, may also be required. The evaluation of patients with suspected vasculitis includes inflammatory markers, antineutrophil cytoplasmic antibody (ANCA), serum complement, cryoglobulins, viral hepatitis screen, and blood cultures (to rule out endocarditis) [5,15].

3.6. Renal toxicity

Renal irAEs occur in 2–5% of patients treated with ICIs, but there is mounting evidence to suggest low-grade kidney injury occurs in up to 29% of patients [16]. Acute interstitial nephritis is the most common renal irAE. Acute thrombotic microangiopathy, minimal change disease, and lupus-like nephritis have also been reported. Onset is typically 2–3 months with CTLA-4 therapy, and 3–10 months with PD-1 therapy [16]. Delayed diagnosis, more than 2 months after ICI cessation, has also been reported.

Renal irAEs are usually detected on routine monitoring of serum creatinine, but oliguria, hematuria, peripheral edema, and anorexia have been reported as presenting symptoms. Other causes of renal impairment, such as dehydration, other drug-induced injury, and infection, should be investigated. Urinalysis and renal ultrasound should be performed. Weekly creatinine monitoring is recommended for grade 1 toxicity, with more frequent testing for grade 2 and higher toxicities. Renal biopsy is recommended for suspected immune-related renal injury. For grade 2 or higher toxicity without another clear source, steroids are recommended. Nephrology consultation is recommended for grade 3 or higher toxicity and considered for grade 2 toxicity.

3.7. Nervous system toxicity

Multiple types of neurologic irAEs involving the central and peripheral nervous systems (CNS and PNS, respectively) can occur. These irAEs can result in permanent neurological deficits or death. Myasthenia gravis, encephalitis, and transverse myelitis are more common with anti–PD-1/anti–PD-L1 therapy. Whereas, Guillain-Barre syndrome and aseptic meningitis are more closely associated with CTLA-4 and combination therapy. Myasthenia gravis has a higher fatality rate and an earlier onset (29 days) than other neurologic irAEs (61–80 days). Severe irAEs tend to occur approximately 45 days from initiation of treatment.

Common symptoms are altered mental status, headaches, seizures, focal neurologic changes, and posterior reversible encephalopathy. Early consultation to neurology is recommended for neurologic irAEs due to the risk of rapid deterioration. There are broad differential diagnoses for patients with neurologic symptoms, including infection, CNS metastasis, leptomeningeal spread, paraneoplastic syndromes, vitamin B12 deficiency, and diabetic neuropathy. Guillain-Barre syndrome should be treated with intravenous immunoglobulin followed, if needed, by plasmapheresis. Neurologic irAEs refractory to systemic steroids may respond to plasmapheresis and intravenous immunoglobulin [1,17].

3.8. Hematologic toxicity

Hematologic irAEs, such as autoimmune hemolytic anemia, acquired thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome (HUS), aplastic anemia, lymphopenia, immune thrombocytopenia (ITP), and acquired hemophilia, can occur with ICI therapy but are very rare. Patients with changes in hematologic parameters on routine blood testing require ongoing evaluation. Persistent or profound cytopenias following ICI initiation requires further evaluation. In addition to complete blood count (CBC), reticulocyte count, and a peripheral blood smear, an assessment for hemolysis should be performed. Unexplained anemia warrants evaluation for GI bleeding, cancer-related etiology, other drug side effects, or hemolysis. Hematology consultation and bone marrow biopsy may be required. Clinicians should also be aware of hemophagocytic lymphohistiocyotosis/macrophage activation syndrome. This clinical syndrome presents with high fever, rash, hepatitis, pancytopenia, and coagulopathy. Neurologic presentations such as confusion and seizure can also occur. Although extremely rare, it is associated with a high mortality risk and typically presents within the first month of ICI initiation.

3.9. Cardiovascular toxicity

Cardiovascular irAEs with ICIs, including myocarditis, pericarditis, cardiac fibrosis, arrhythmias, and heart failure, are more common with combination ICI therapy. Myocarditis occurs in 1% of patients treated with ICIs, at a median onset of 34 days after ICI initiation, and is often associated with other irAEs, such as myasthenia gravis and myositis [18].

Baseline electrocardiogram (EKG) and fasting lipids are recommended prior to ICI initiation. Troponin, brain natriuretic peptide (BNP) or pro-BNP, and total CK can also be considered to identify high-risk patients [20]. Patients with abnormal baseline testing may benefit from interval surveillance with EKGs and cardiac biomarkers [9]. Common presenting symptoms are chest pain, shortness of breath, and acute cardiovascular collapse. Vague symptoms include fatigue and weakness, which are also common at presentation. Evaluation for suspected cardiac irAE includes EKG, chest imaging to rule out a pulmonary source, cardiac biomarkers, and consultation to cardiology. Due to the risk of rapid progression and death, patients with suspected myocarditis should be admitted to the hospital and started on systemic steroid therapy with consultation to cardiology.

3.10. Ocular toxicity

Ocular toxicity is rare with ICI therapy (<1%). There have been a few case reports of uveitis, peripheral ulcerative keratitis, episcleritis, and blepharitis, with a median onset of 2 months [19]. Presentation can include floaters, conjunctival injection, and worsening vision. Ocular toxicity may occur with other irAEs, such as colitis. A basic eye chart exam, pupil examination, assessment of color vision, and red reflex can be performed. Untreated ocular toxicity can result in blindness; therefore, new visual complaints (red, painful, dry eyes, or visual changes) must be expeditiously evaluated by ophthalmology. Initiation of steroids is best deferred until after ophthalmologic evaluation, as the steroids may worsen symptoms if they are due to an infectious etiology.

Table 5
Immune checkpoint inhibitor re-challenge recommendations following CTCAE v5.0 graded irAE toxicity.

Organ system toxicity	*Re*-challenge?				
	G1	G2	G3	G4	Comment
Cardiovascular					
Myocarditis	N/A	N	N	N	
Gastrointestinal					
Colitis	Y	Y	?	N	Management differences between CTLA-4 vs PD-1
Hepatitis	Y	Y	?	N	
Pulmonary					
Pneumonitis	Y	Y	N	N	
Sarcoidosis[&]	N/A	?	?	?	[&]Scant data on ICI-related sarcoidosis
Musculoskeletal/Rheumatologic					
Inflammatory arthritis	Y	Y	Y	N	
Infusion reactions	Y	Y	N	N	
Nervous system					
Encephalitis	Y	N	N	N	
Transverse myelitis	N	N	N	N	
Neuropathy sensory	Y	Y	N	N	
Myasthenia Gravis	Y	N	N	N	
Guillain Barre	N	N	N	N	
Pancreatic					
Amylase/lipase	Y	Y	N	N	
Skin					
Rash/dermatitis/pruritus	Y	Y	Y	N/A	
Bullous disease	Y	Y	?	N	Stevens-Johnson syndrome, SCAR or TENS, no re-challenge
Endocrine					
Hypothyroidism	Y	Y	Y	Y	In most cases it is reasonable to continue therapy while providing disorder-specific supportive therapy.
Hyperthyroidism	Y	Y	Y	Y	
Hypophysitis	Y	Y	Y	Y	
Type 1 diabetes	Y	Y	Y	Y	
Renal					
Nephritis	Y	Y	?	N	
Proteinuria	Y	Y	N	N	
Hematologic					
Anemia/thrombocytopenia	Y	Y	Y	N	
Ophthalmologic					
Uveitis	Y	Y	N	N	
Episcleritis	Y	Y	N	N	
*Blepharitis	Y	Y	Y	Y	*Not defined in CTCAE

G = grade; N/A = not applicable; Y = yes; N = no;? = consider consultation with specialist; SCAR = severe cutaneous adverse reaction; TENS = toxic epidermal necrolysis syndrome; ICI = immune checkpoint inhibitor; PD-1 = programmed cell death protein 1; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4.

4. Special considerations

ICI therapy may exacerbate a pre-existing autoimmune disease. In this setting, the potential benefits of ICI therapy must be carefully weighed against the nature and potential consequences of such a flare up. Similarly, sound clinical decision making is essential when considering rechallenging a patient who has experienced an irAE with an ICI [5,9,20]. Both patient groups should be monitored very closely. Clinicians should incorporate tumor response assessment into the clinical decision-making process, weighing the benefits of prior objective and sustained response against the risk of toxicity with rechallenge. Permanent discontinuation is indicated in most cases of severe irAEs, in some moderate cases, and in irAE reoccurrences after resumption of the ICI. If a severe toxicity occurs with CTLA-4 therapy, the resumption of ICI therapy with an anti-PD-1/PD-L1 therapy may be considered after the irAE has been completely resolved. Early consultation with organ-specific specialists and immunotherapy/rheumatologic specialists for irAE toxicity management and decision making for rechallenge are critical. Table 5 summarizes rechallenge recommendations by irAE, and Table 6 provides additional ICI adverse event management resources.

Table 6
Additional immune checkpoint inhibitor adverse event management resources.

Resource	Reference
American Society of Clinical Oncology Clinical Practice Guideline: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy	Schneider, B.J., et al. (2021). Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol, 2021. doi: https://doi.org/10.1200/-JCO.21.01440
European Society of Medical Oncology Clinical Practice Guidelines: Management of toxicities from immunotherapy	Haanen, J.B.A.G. et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2017. 1;28(Suppl 4): iv119-iv142.†
Society for Immunotherapy of Cancer Clinical Practice Guideline: Immune checkpoint inhibitor–related adverse events	Brahmer J.R., et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer, 2021. 9 (6):e002435.
Sociedad Espanola de Oncologia Medica Clinical Guideline (2019): Management of immune-related adverse events in patients treated with immune checkpoint inhibitors	Majem, M., et al. SEOM clinical guideline for the management of immune-related adverse events in patients treated with immune checkpoint inhibitors. Clin Transl Oncol, 2020. 22:213–222.
Multinational Association of Supportive Care in Cancer Recommendations (2020): Management of immune-related adverse events of patients undergoing treatment with immune checkpoint inhibitors	Rapoport, B.L., et al. MASCC 2020 recommendations for the management of immune-related adverse events of patients undergoing treatment with immune checkpoint inhibitors. Support Care Cancer, 2020. 28:6107–6110.
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities, Version 1.2022	Thompson, J.A., et al., NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2022. J Natl Compr Canc Netw, 2022. **20**(4): p. 387–405.

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Declaration of Competing Interest

Dr. O'Cearbhaill reports honoraria from GSK, Bayer, Regeneron, Immunogen, MJH, SeaGen, Fresenius Kabi, and Curio, all outside the submitted work.

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