Asia-Pacific Journal of Oncology Nursing 11 (2024) 100549

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.apjon.org

Review

Updates and emerging trends in the management of immune-related adverse events associated with immune checkpoint inhibitor therapy

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ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Pembrolizumab
Nivolumab
Ipilimumab
Immune-related adverse events

ABSTRACT

The rapidly expanding class of therapies targeting immune checkpoints for the treatment of various cancers now includes 8 clinically approved agents: a lymphocyte-activation gene 3 (LAG-3) inhibitor (relatlimab), a cytotoxic T lymphocyte associated protein 4 (CTLA-4) inhibitor (ipilimumab), three programmed cell death protein 1 (PD-1) inhibitors (nivolumab, pembrolizumab and cemiplimab), and three programmed cell death ligand-1 (PD-L1) inhibitors (atezolizumab, durvalumab, and avelumab). Previously, we reviewed the mechanisms of immune-related adverse events (irAEs), strategies for management of irAEs, and highlighted similarities as well as differences amongst clinical guidelines from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), Society for Immunotherapy of Cancer (SITC), and European Society for Medical Oncology (ESMO). Herein, we provide an update that includes discussion of changes to these clinical guidelines since our last review, the new LAG-3 targeted agents, emerging patterns of irAEs, and new directions for improved monitoring and treatment of irAEs that could incorporate interdisciplinary pharmacist-led teams, artificial intelligence, and pharmacogenomics.

Immune checkpoints in cancer

The pioneering of modern cancer immunotherapy is commonly attributed to Dr. William Coley, who used intratumoral injections of inactivated *Streptococcus pyogenes* and *Serratia marcescens* bacteria strains to stimulate immune responses against cancer.[1] This later paved the way for the approval of recombinant interleukin-2, an immunostimulatory cytokine that increased immune responses against a patient's cancer, for the treatment of renal cell carcinoma and melanoma.[2] However, it remained unknown as to why the immune system needed to be activated in order to eradicate cancer cells. The works of Drs. James Allison and Tasuku Honjo on cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), respectively, shed light on the molecular mechanisms that act as brakes on the immune system and prevent it from doing its job.[3] T-cell recognition and activation against tumor antigens require both binding of T-cell receptors (TCR) to antigen peptides presented in the context of major histocompatibility complex (MHC) and engagement of the co-stimulatory receptor CD28 on T-cells with CD80/86 on antigen-presenting cells or tumor cells.[4] However, antitumor immunity may be suppressed through activation of immune checkpoints. These 'immune checkpoints' were expressed on tumor cells, allowing them to escape detection by shutting down immunosurveillance and immune attack.[5] Successful targeting and inhibition of these immune checkpoint pathways was found to prolong progression-free and overall survival in cancer patients and currently, there are 8 immune checkpoint inhibitors approved for the treatment of cancer (Table 1).[6] Although there are many immune checkpoints, only CTLA-4, PD-1/programmed cell death ligand-1 (PD-L1), and lymphocyte-activation gene 3 (LAG-3) are proven therapeutic targets in cancer patients (Fig. 1).[7,8]

Cytotoxic T-lymphocyte-associated protein 4 is a co-inhibitory receptor constitutively expressed on Tregs that competes with CD28, a co-stimulatory receptor, for binding to CD80/86 on T cells.[4] Activation of the CTLA-4 pathway leads to T-cell anergy instead of T-cell activation that results when CD28 binds to CD80/86.[8–10] Tregs also inhibit antigen presentation by antigen presenting cells (APCs) in the tumor milieu and its draining lymph nodes.[11] In addition, Tregs can also express other immune checkpoint molecules such as PD-1,[12–14] an anti-CTLA-4 antibody, entered clinical trials in 2000 and was first approved in 2011 for melanoma.[1] Its first phase III clinical trial, in previously treated advanced melanoma patients, showed an overall response rate in patients receiving ipilimumab alone was 10.9%, with a median OS of 10.1 months, and 60% of responders maintained their response for at least two years.[15] This

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https://doi.org/10.1016/j.apjon.2024.100549
Received 23 April 2024; Accepted 26 June 2024

Table 1
Currently approved immune checkpoint inhibitors.[6]

Generic name	Trade name	Target	Indication (Approval year)
Pembrolizumab	Keytruda	PD-1	Melanoma, non-small cell lung cancer (2018), head and neck squamous cell cancer (2018), classical Hodgkin Lymphoma (2018), primary mediastinal large B-cell lymphoma (2018), urothelial carcinoma (2018), microsatellite instability-high cancer (2018), gastric cancer (2018), cervical cancer (2018), hepatocellular carcinoma (2018), Merkel cell carcinoma (2018) (Merck 2018; FDA 2018)
Nivolumab	Opdivo	PD-1	Metastatic small cell lung cancer (2018), unresectable or metastatic melanoma (2017), locally advanced or metastatic urothelial carcinoma (2017), adult and pediatric patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer (2017), hepatocellular carcinoma (2017), metastatic non-small cell lunch cancer (2016), advanced renal cell carcinoma (2016), classical Hodgkin lymphoma (2016), recurrent or metastatic squamous cell carcinoma of the head and neck (2016) (FDA 2018; Squibb 2018)
Cemiplimab	Libtayo	PD-1	Metastatic CSCC (2018), locally advanced CSCC (2018) (FDA 2018; Regeneron Pharmaceuticals 2018)
Atezolizumab	Tecentriq	PD-L1	Urothelial carcinoma (2016), metastatic non-small cell lung cancer (2016) (FDA 2018; Genentech 2018)
Avelumab	Bavencio	PD-L1	Metastatic Merkel cell carcinoma (2017), locally advanced or metastatic urothelial carcinoma (2017) (FDA 2018; EMD Serono 2018)
Durvalumab	Imfinzi	PD-L1	Unresectable stage III non-small cell lung cancer (2018), locally advanced or metastatic urothelial carcinoma (2017) (FDA 2018; AstraZeneca 2018)
Ipilimumab	Yervoy	CTLA-4	Advanced renal cell carcinoma (2018), adults and pediatric with microsatellite instability-high or mismatch repair deficient (2018) metastatic colorectal cancer (2018), cutaneous melanoma (2015), unresectable or metastatic melanoma (2014) (FDA 2018; Squibb 2018)
Relatlimab	Opdualag	LAG-3	Unresectable or metastatic melanoma (2022) (Chocarro, Bocanegra et al., 2022[9])

PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; CTLA-4, cytotoxic T lymphocyte associated protein 4; LAG-3, lymphocyte-activation gene 3; FDA, Food and Drug Administration; CSCC, cutaneous squamous cell carcinoma.

durable response expanded on the previously seen success of IL-2, showing the short- and long-term promise of immune checkpoint inhibition.

Programmed cell death 1 receptor expression starts during $CD4^{-}CD8^{-}$ T cell maturation in the thymus and can be further expressed in $CD4^{+}$ or $CD8^{+}$ T cells, NK T cells, monocytes, B cells, and dendritic cells.[13,16] Its expression is modulated in normal tissues to avoid damage by the immune system[17] and it is not normally found in circulating T cells, but expression is induced by T cell receptor activation or cytokine stimulation.[10] The binding of PD-1 to its ligands, PD-L1 or PD-L2, on antigen-presenting cells or tumor cells results in inhibition of T-cell proliferation and reduction in cellular survival,[4] T cell anergy,[16] and inhibition of cytokine release.[13] The interaction between PD-1 and PD-L1 or PD-L2 plays an important role in maintaining an adequate balance between T cell activation and tissue damage against self-antigens.[12,13] While normal tissues rarely express these inhibitory ligands, tumor cells have the ability to overexpress them, using this mechanism to evade the immune cells and reduce anti-tumor response,[12,13,16] thereby facilitating tumor growth.[12] The first PD-1 inhibitor approved by the Food and Drug Administration (FDA) was pembrolizumab[18] in September of 2014, and subsequently two additional PD-1 inhibitors (nivolumab[19] and cemiplimab[20]) and three PD-L1 inhibitors (atezolizumab[21], durvalumab[22], and avelumab[23]) were approved (Table 1). The PD-1/PD-L1 inhibitors are now the largest and most widely used of the immune checkpoint targeted therapies, with first-line indications in non-small cell lung cancer, melanoma, and urothelial carcinoma.

LAG-3 has similar activity as CTLA-4 by inhibiting TCR signaling pathway.[24] The expression of LAG-3 can be found on activated $CD4^{+}$ and

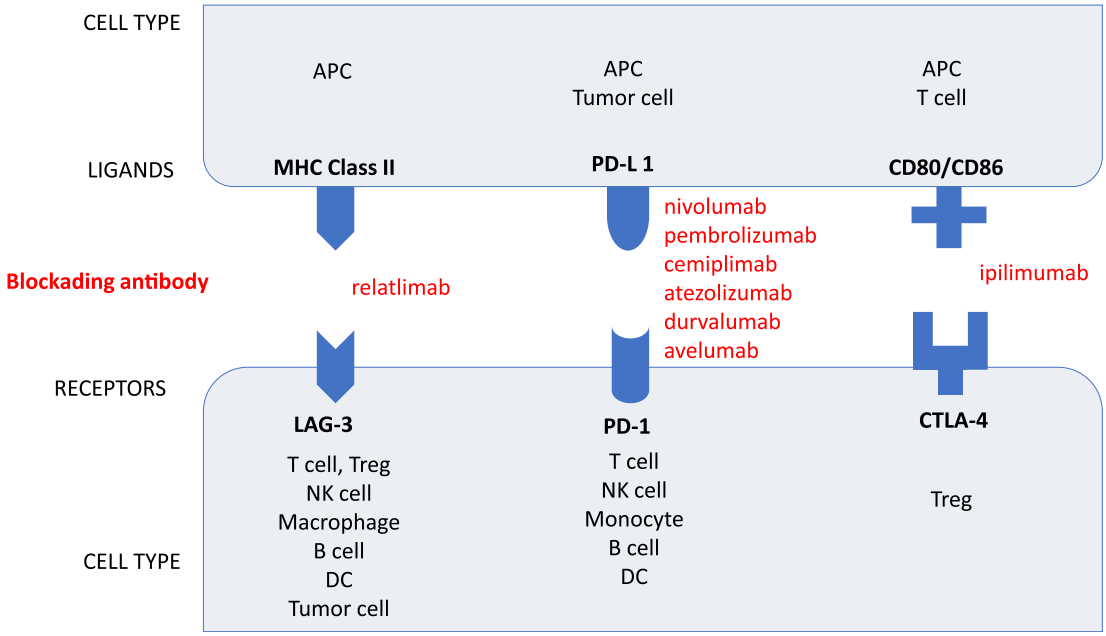

Fig. 1. Simplified schema of therapeutically targeted immune checkpoint pathways. PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; CTLA-4, cytotoxic T lymphocyte associated protein 4; LAG-3, lymphocyte-activation gene 3; APC, antigen presenting cell; DC, dendritic call, MHC, major histocompatibility complex, Treg, regulatory T cell; NK, natural killer.

$CD8^+$ T cells, Tregs, natural killer (NK) cells, B cells, plasmacytoid dendritic cells, and tumor-associated macrophages (TAMs), and it is upregulated in many tumor cells.[24,25] LAG-3 binds with higher affinity to stable MHC-II/peptide complexes on APCs than CD4, blocking TCR-CD4 binding, and consequently impairing T-cell function while its cross-linking with CD3 diminishes T-cell proliferation.[24] It also down-modulates TCR-CD3 intracellular signal transduction cascades and calcium fluxes within the immunological synapse, terminating cytokine and T cell responses to the TCR-CD3 activation while favoring CD4 and CD8 T cell exhaustion.[9] Moreover, LAG-3 expression on Tregs is crucial to their immunosuppressive activity.[24] T cells can express LAG-3 concomitantly with PD-1,[24,26] suggesting that blockade of both checkpoints may enhance anti-tumor effects. Pre-clinical investigations verified the synergistic enhancement of therapeutic response in melanoma with dual blockade of LAG-3 and PD-1,[27,28] and subsequent clinical trials resulted in the approval of relatlimab in combination with nivolumab by the FDA in 2022 for unresectable or metastatic melanoma.[26,29]

In the absence of cancer, CTLA-4, LAG-3, and PD-1 serve to regulate the interaction between T-cells and self- versus non-self-antigens.[9] Therefore, their inhibition can lead to the activation of autoreactive T-cells resulting in the unique immune-related adverse events (irAEs) associated with immune checkpoint inhibitors[30] (Fig. 2). As a result, the management of irAEs differs significantly from the management of adverse events from cytotoxic chemotherapy. Previously, we reviewed the mechanisms of irAEs, strategies for management of irAEs, and highlighted similarities as well as differences amongst clinical guidelines from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), Society for Immunotherapy of Cancer (SITC), and European Society for Medical Oncology (ESMO). Herein, we provide an update that includes discussion of changes to these clinical guidelines[31–34] since our last review, the new LAG-3 targeted agents, emerging patterns of irAEs, and new directions for improved monitoring and treatment of irAEs that could incorporate interdisciplinary pharmacist-led teams, artificial intelligence, and pharmacogenomics.

Patterns of immune-related adverse events

A meta-analysis comparing the PD-1 inhibitors nivolumab and pembrolizumab to cytotoxic chemotherapy found that immunotherapy had significantly fewer adverse events overall compared to cytotoxic chemotherapy.[35] However, the types of adverse events were markedly different between immune checkpoint inhibitor therapy and chemotherapy.[35] There was more asthenia, fatigue, nausea, diarrhea, and decreased appetite with immune checkpoint inhibitor therapy while chemotherapy was associated with more neutropenia, anemia, alopecia, stomatitis, and myalgia.[35]

These findings suggest that immune checkpoint inhibitors are generally more tolerable than cytotoxic chemotherapy. However, adverse events associated with immunotherapies may affect any organ system and are referred to as irAEs.[36] The incidence of irAEs varies by

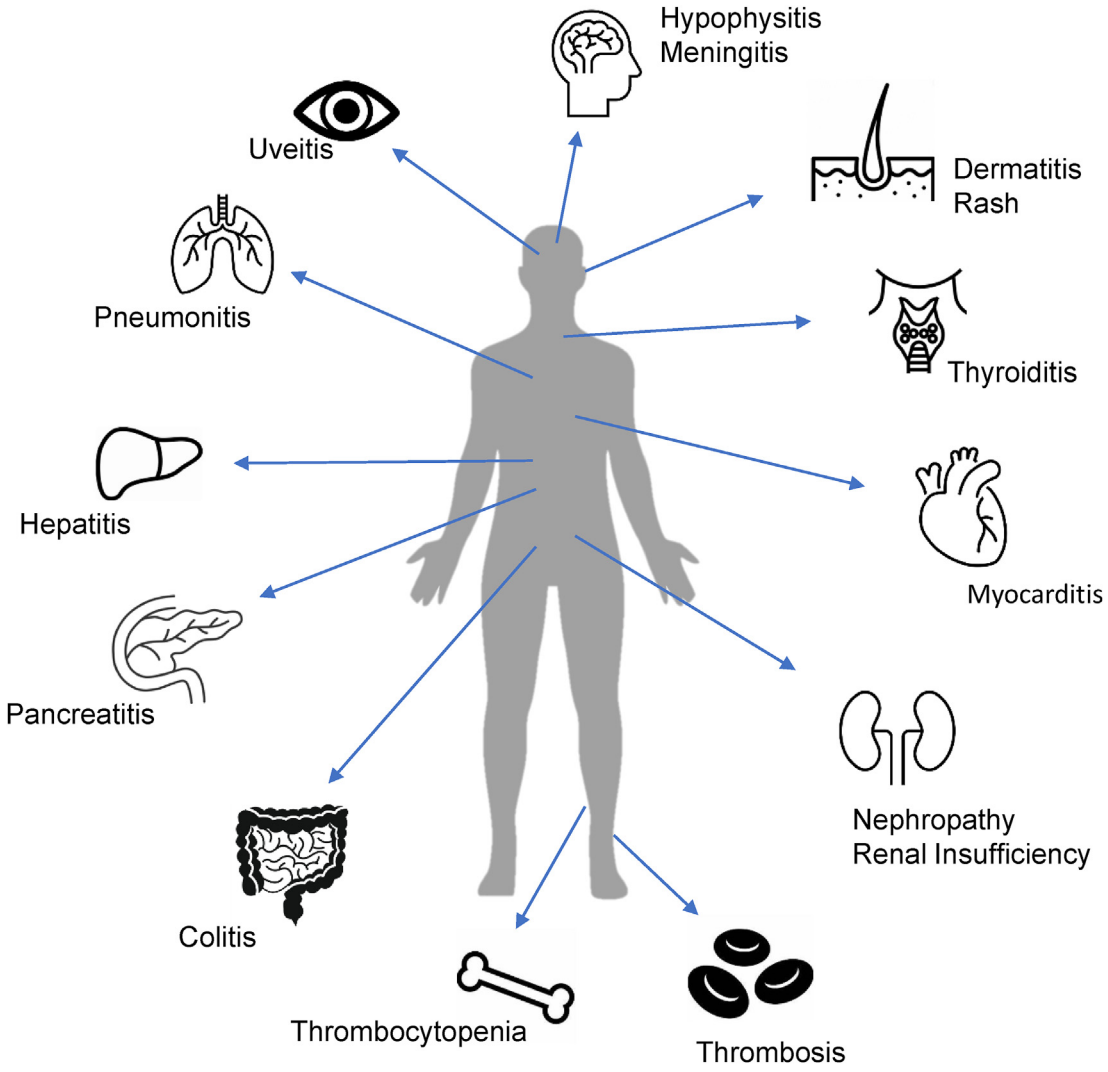

Fig. 2. Major immune-related adverse events associated with immune checkpoint inhibitor.

immune checkpoint inhibitor (ICI) class. CTLA-4 inhibitors generally have higher rates and higher severity of irAEs than PD-1/L1 and LAG-3 inhibitors.[9,36] PD-1/PD-L1 Inhibitors generally have a lower incidence of irAEs, the most common of which include dermatologic effects, fatigue, and endocrine toxicity. Severe irAEs occur in only about 10% of patients receiving PD-1/PD-L1 inhibitors.[37] Adverse effects observed with the LAG-3 inhibitor (relatlimab) include musculoskeletal pain, fatigue, pruritus, and diarrhea but notably relatlimab is only used in combination with nivolumab.[9] Furthermore, there appears to be a correlation between certain toxicities and specific types of cancers such as vitiligo in melanoma patients.[38]

The irAEs often manifest in a dose-dependent manner within 3–6 months of initiation of CTLA-4 or PD-1/PD-L1 inhibitor therapy although they have been reported to occur up to a year after the patient is exposed to PD-1 inhibitors.[38] Development of irAEs is unpredictable and does not appear to correlate with cumulative dose toxicity or anticancer efficacy.[39] Combining immune checkpoint inhibitor therapies increases the incidence and severity of irAEs (ASCO 2022[32]). The irAEs can persist even after immunotherapy is paused, with some patients experiencing chronic irAEs for over five months.

New patterns and types of irAEs include polymyalgia rheumatica-like symptoms, small joint symmetric inflammatory arthritis, and large joint asymmetric oligoarthritis.[40] Factors such as age, body mass index (BMI), gender, and smoking history can influence the risk of developing irAEs. For instance, a higher risk of irAE is associated with age under 60 years, high BMI, women on CTLA4, and men on PD-1/PD-L1 agents.[41]

Management of irAEs

Immune-related adverse events are managed according to severity assessed using the Common Terminology Criteria for Adverse Events (CTCAE) grading system (CTEP 2018)[42], and summarized in Table 2. Corticosteroids are the mainstay for low severity irAEs (e.g., grades 1–2), administered at low (0.5–1 mg/kg/day), moderate (1–2 mg/kg/day), or high dosages ($\geq$ 2 mg/kg/day). After the resolution of irAEs, the patient will require tapering off corticosteroid therapy. Other immunosuppressants may be considered if the irAEs are severe (e.g., grades 3–4) or when irAEs are not resolved with the use of corticosteroids. In general, immune checkpoint inhibitor therapy may be continued while most grade 1 events are managed. For grade 2–4 events, immunotherapy is usually withheld and can be re-initiated once irAEs are resolved, although permanent discontinuation is sometimes warranted. The similarities and differences amongst the clinical guidelines for the management of specific irAEs are discussed below.

Dermatologic

Dermatologic toxicities are the most common irAEs associated with immune checkpoint inhibition and can affect up to 50% of patients, the majority of which are of low-grade severity. Typical presentations include pruritus, rash, dermatitis, and bullous dermatitis. However, potentially fatal skin reactions such as Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported.

The NCCN, ASCO, ESMO, and SITC guidelines all recommend the use of topical steroids, oral antihistamines, and topical emollients for low-grade rash/inflammatory dermatitis. For grade 1 cases, ASCO, NCCN, and SITC recommend continuing ICI therapy with appropriate monitoring and intervention while ESMO emphasizes individualized management based on toxicity severity and patient factors. For grade 2 dermatitis, all the guidelines recommend that clinicians consider holding therapy and starting medium to high potency corticosteroids until symptoms reduce to grade 1 before reinitiating ICI therapy. A dermatological referral is warranted in these patients if symptoms persist. Any cases of grades 3 or 4 dermatitis require immediate discontinuation of immune checkpoint inhibitors and treatment with high-dose systemic corticosteroids until severity is less than or equal to grade 1, at which time immune checkpoint inhibitors may be re-challenged. NCCN and SITC recognize pruritus as an irAE and recommend similar management as with rash/inflammatory dermatitis. For Grade 3 pruritis, the addition of gamma-aminobutyric acid (GABA) agonists (e.g., pregabalin or gabapentin) may be helpful.

For bullous dermatitis, NCCN guidelines recommend holding immune checkpoint inhibitors and starting high-potency topical steroids for grade 1 bullous dermatitis whereas ASCO guidelines recommend continuing therapy along with local wound care. For grade 2 and above, both guidelines recommend high-dose oral or intravenous corticosteroids and discontinuation of immune checkpoint inhibitors therapy, along with wound care and topical corticosteroids. Severe skin reactions such as SJS and TEN can be fatal and the consensus recommendation is high-dose corticosteroids with inpatient care and permanent discontinuation of immune checkpoint inhibitors.

Gastrointestinal

Gastrointestinal irAEs are divided into three major categories: colitis, hepatitis, and pancreatitis. Colitis usually presents as diarrhea and can affect up to 44% of patients, depending on the immune checkpoint inhibitor regimen. For grade 1 colitis, all guidelines recommend close monitoring, changes in diet, and continuation of immune checkpoint inhibitor therapy. Loperamide may be used, however, other causes such as *Clostridium difficile* infection need to be ruled out. For grade 2 reactions, it is generally recommended to hold immunotherapy and start high-dose systemic corticosteroids. A gastrointestinal consult is recommended for grade 2 toxicity and a negative infectious stool culture. At grade 3 or above, inpatient hospitalization is warranted and the addition of an immunosuppressant such as infliximab should be considered.

Up to 30% of patients receiving immune checkpoint inhibitors can develop hepatitis that usually presents as transaminitis (diagnosed by increased blood levels of alanine transaminase and aspartate transaminase), with or without hyperbilirubinemia. Transaminitis should be evaluated to rule out viral causes, disease or drug-related hepatic dysfunction, and hepatotoxic medications. Serial labs assessing blood levels of liver transaminases and bilirubin are necessary to monitor and assess recovery. Grade 1 hepatitis should be monitored and all guidelines recommend continuing immune checkpoint inhibitor therapy. For those with grade 2 or above, immune checkpoint inhibitors therapy should be discontinued and high-dose corticosteroids initiated. If there is no improvement after 3 days (i.e., steroid refractory), mycophenolate mofetil should be considered. Importantly, infliximab should not be used for hepatitis since it is associated with hepatotoxicity. Permanent discontinuation of immune checkpoint inhibitors is recommended for grade 4 hepatitis, and patients should be treated inpatient.

Pancreatitis presents with elevations in amylase/lipase in addition to clinical symptoms. According to NCCN guidelines, patient assessment should include an abdominal computed tomography (CT) with contrast, and consider magnetic resonance cholangiopancreatography if clinical suspicion of pancreatitis is present with no radiological evidence on CT. A gastroenterology consult should be considered for all grades. Immunotherapy should be held for grades 2 and 3, and management should be as per elevation in amylase/lipase (asymptomatic) for grade 2. For grades 3, give corticosteroids, and permanently discontinue immunotherapy for grade 4.

Endocrine

NCCN, ASCO, ESMO, and SITC all recognize new-onset hyperglycemia as an irAE. Patients with grade 1 hyperglycemia (fasting blood glucose <200 mg/dL) and/or a history of type 2 diabetes mellitus with low suspicion of diabetic ketoacidosis, may continue immunotherapy along with monitoring of blood glucose and dietary or lifestyle modifications as needed. If hyperglycemia with fasting blood glucose > 200 mg/dL or random blood glucose > 250 mg/dL, or if there is a history

Table 2
General approach for management of irAEs.

irAE	ICI Therapy	Immunosuppressants	Symptom-specific Treatment
Grade 1	Discontinue if hyperthyroidism, including thyrotoxicosis, or pneumonitis Consider holding if renal, hypophysitis, sarcoidosis Hold if neurologic, aplastic anemia, acquired hemophilia Continue for all others	Prednisone 0.5–1 mg/kg/day if acquired hemophilia	Topical steroids[a], oral antihistamines[b], topical emollients if dermatologic Loperamide if gastrointestinal[c] Thyroid hormone supplementation[d] if hypothyroidism Beta-blockers for symptomatic hyperthyroidism[e]; Insulin therapy if hyperglycemia hormone replacement therapy[f] if hypophysitis Consider artificial tears if ocular Analgesics[g] if rheumatologic
Grade 2	Considering holding if dermatologic, rheumatologic, or lymphopenia Hold for all others	Prednisone 0.5–1 mg/kg/day[h] Prednisone 1–2 mg/kg/day if hypophysitis[i] Prednisone 1 mg/kg/day or pulse-dose methylprednisolone (1 g/day for 3–5 days) if transverse myelitis[k]	In addition, consider: Adding infliximab if gastrointestinal[j] Empiric antibiotics if pulmonary Adding ATG and cyclosporine if aplastic anemia Adding GABA agonist[l] or duloxetine for pain if peripheral neuropathy Adding ophthalmic prednisone if ocular
Grade 3	Discontinue if hepatitis, renal, ocular, pulmonary, neurologic, cardiovascular, rheumatologic, and/or hematologic Hold for all others	Prednisone 1–2 mg/kg/day Methyl prednisolone 2–4 mg/kg/day if peripheral neuropathy or Guillain-Barre syndrome Consider plasmapheresis, intravenous immunoglobulin therapy, methotrexate, azathioprine, or mycophenolate mofetil through grade 4 if myositis; Consider methotrexate or tocilizumab through grade 4 if *rheumatoid arthritis Consider rituximab or cyclophosphamide if acquired hemophilia	In addition, consider: Adding omalizumab, GABA agonist[l] if pruritus plasmapheresis or immunoglobulin if neurologic pyridostigmine[m] if myasthenia gravis Antirheumatic drugs[n], methotrexate, infliximab or tocilizumab if refractory arthritis or polymyalgia-like syndrome infliximab, mycophenolate mofetil, intravenous immunoglobulin if pulmonary or renal rituximab if autoimmune encephalopathy infliximab if cardiovascular[o] Adding rituximab or dupilumab for bullous dermatitis if no improvement after 3 days
Grade 4	Discontinue	Prednisone 2–4 mg/kg/day	In addition, consider: Adding mycophenolate mofetil if hepatitis[p] Empiric antivirals[q] if aseptic meningitis and/or encephalitis rituximab if acquired TTP[r] rituximab or cyclophosphamide if acquired hemophilia rituximab, intravenous immunoglobulin, cyclosporine A, or mycophenolate mofetil if autoimmune hemolytic anemia eculizaumab[s] if hemolytic uremic syndrome Intravenous immunoglobulin, rituximab, or thrombopoietin receptor agonists if immune thrombocytopenia IVIG (1 g/kg/day in divided doses per package insert for 3–4 days) for SJS or TEN Adding infliximab or ATG for cardiac irAEs if no improvement is noted within 24 hours

[a] Clobetasol dipronate 0.05% or equivalent.
[b] Cetirizine, hydroxyzine, or equivalent.
[c] Avoid for *Clostridium difficile*.
[d] Levothyroxine 1.6 mcg/kg or 25–50 mcg in elderly.
[e] Atenolol 25–50 mg.
[f] Thyroid, testosterone, estrogen.
[g] Acetaminophen or nonsteroidal anti-inflammatory drugs.
[h] Consider starting at 1 mg/kg/day if gastrointestinal.
[i] Consider infliximab, MMF, tacrolimus, or loperamide through grade 4.
[j] Infliximab-refractory is noted if no response is seen in 2 days.
[k] Intravenous immunoglobulin or plasmapheresis is strongly recommended.
[l] Gabapentin, pregabalin, or equaivalent if neuropathic-related.
[m] Pyridostigmine 30 mg three times a day.
[n] Sulfasalazine, methotrexate, leflunamide.
[o] High dose prednisone for myocarditis.
[p] Avoid infliximab for hepatitis.
[q] Intravenous acyclovir.
[r] Prednisone 1 g intravenously for TTP.
[s] Eculizumab 900 mg weekly for four doses, 1200 mg week 5, then 1200 mg every 2 weeks.

irAEs, immune-related adverse events; ICI, immune checkpoint inhibitor; ATG, anti-thymocyte globulin; GABA, gamma-aminobutyric acid; TTP, thrombotic thrombocytopenic purpura; IVIG, intravenous immunoglobulin; SJS, Steven Johnson Syndrome; TEN, Toxic Epidermal Necrolysis.

of type 2 diabetes mellitus with fasting/random glucose >250 mg/dL, then consider holding immunotherapy until hyperglycemia is controlled. Oral therapy or insulin should be initiated to treat low-grade hyperglycemia; however, management should be started with insulin therapy for grades 3 or 4. ESMO guidelines also recommend inpatient care for grade 3 to 4 hyperglycemia. An endocrinologist should be consulted if the patient is symptomatic and blood glucose is uncontrolled. SITC guidelines specifically address type 1 diabetes mellitus and recommend holding immunotherapy and management with insulin.

For hypothyroidism, both NCCN and SITC guidelines recommend thyroid hormone supplementation with monitoring of TSH and free T4 levels every 4–6 weeks, for any grade event whereas ESMO and ASCO recommend thyroid hormone therapy in symptomatic patients. In general, immunotherapy may be continued for grade 1 or asymptomatic hypothyroidism, and grade 2 events should be handled based on the specific patient scenario since the guidelines diverge with regard to whether or not to hold immunotherapy. Immune checkpoint inhibitors should be held for grade 3–4 events until symptoms resolve.

Hyperthyroidism, including thyrotoxicosis, is recognized by ASCO, ESMO, and SITC. For grade 1, ASCO and SITC suggest continuing immunotherapy along with symptomatic treatment with beta-blockers as needed, whereas ESMO and NCCN suggest holding immunotherapy and restarting immunotherapy when asymptomatic. For grades 2–4, all guidelines recommend holding immunotherapy until symptoms return to baseline, with the administration of a beta blocker for supportive care. Monitoring should include thyroid function tests every 4–6 weeks until recovery. If TSH >10, this could indicate the development of hypothyroidism requiring the administration of thyroid replacement therapy.

Hypophysitis, inflammation of the anterior lobe of the pituitary gland, is recognized by all four guidelines. ASCO and SITC suggest holding immunotherapy while NCCN and ESMO suggest continuing ICI therapy with appropriate HRT for grade 1 hypophysitis. All guidelines recommend holding immune checkpoint inhibitors until resolution of the irAE for grades 2–4, and administer supportive care (e.g., oral fluids, loperamide, avoidance of high fiber and lactose diet), and hormone replacement therapy (e.g., thyroid, testosterone, estrogen) as needed. Recommendations for the administration of corticosteroids vary between the guidelines; corticosteroids may be initiated for grade 1 (NCCN) or grade 2 (ASCO and ESMO) for moderate symptoms.

Pulmonary

Pneumonitis is recognized by NCCN, ASCO, ESMO, and SITC as an irAE. For any grade pneumonitis, immunotherapy should be discontinued. Grade 2 pneumonitis should be treated with corticosteroids and empiric antibiotics (NCCN, ASCO, and ESMO). SITC guidelines similarly recommend starting corticosteroids but not empiric antibiotic treatment for grade 2 events. For grades 3 to 4, all guidelines suggest permanently discontinuing immunotherapy. If patients do not improve on corticosteroid therapy after 48 hours, then infliximab, mycophenolate mofetil, or intravenous immunoglobulin may be added. Severe pneumonitis (grades 3 or 4) may require inpatient care and infectious workup is warranted (NCCN).

Sarcoidosis is a rare pulmonary toxicity in patients receiving immune checkpoint inhibitors. SITC is the only guideline that addresses sarcoidosis and management is based on clinical experience and case reports. Sarcoidosis occurs at a mean of 9 months following the start of ICI treatment, and symptoms resolve within a mean of 4 months. Sarcoidosis is usually asymptomatic and may mimic progressive disease, especially with lymph node involvement, thus biopsy may be considered in the differential.

Renal

Renal adverse events may occur in 2%–5% of patients. These irAEs were reported within the first 3–10 months of anti-PD1 therapy and within 2–3 months of anti-CTLA4 therapy. Renal toxicities may present as oliguria, hematuria, peripheral edema, and anorexia. Patients with grade 1 events may continue immune checkpoint inhibitors with close monitoring. However, patients with grade 2 to 3 events should hold immune checkpoint inhibitors and initiate low to moderate doses of corticosteroids. Immune checkpoint inhibitor treatment may resume when renal events resolve. Patients with grade 4 toxicities should prompt the permanent discontinuation of immune checkpoint inhibitors and initiation of moderate-dose corticosteroids. Persistent grade 2 or higher toxicities should involve a nephrology consult. SITC recommends that patients with recurrent toxicities receive prophylactic corticosteroids following immune checkpoint inhibitor administration.

Ocular/ophthalmic

Ophthalmic irAEs have an incidence of <1%. These toxicities may present as vision changes, optic nerve swelling, uveitis/irisitis, episcleritis, and/or blepharitis. For grade 1 patients, immune checkpoint inhibitors may be continued. Grade 2 patients should hold immune checkpoint inhibitor therapy. For grades 3 to 4, immune checkpoint inhibitors therapy should be permanently discontinued. Artificial tears are recommended for all grades, and ophthalmic and systemic corticosteroids may be considered starting with grade 2 or higher events. A complete ophthalmic evaluation is recommended within a few days of symptom onset, and SITC also suggests the treatment of ophthalmic irAEs with corticosteroids. ICIs should be withheld until an eye exam is conducted by an ophthalmologist unless systemic steroids are needed for non-ophthalmological issues.

Nervous/neurologic

Neurologic irAEs are uncommon and the incidence of grade 3 or higher events is less than 1%. These toxicities include myasthenia gravis, Guillain-Barre syndrome, peripheral neuropathy, aseptic meningitis, encephalitis, and transverse myelitis, and immune checkpoint inhibitors should be held for any grade event. In the case of myasthenia gravis, immune checkpoint inhibitors should be discontinued, and systemic corticosteroids should be initiated. Pyridostigmine should be administered once the immune checkpoint inhibitor is held. Immune checkpoint inhibitors should be permanently discontinued for patients with grades 3–4 neurologic irAEs, and moderate to high doses of corticosteroids should be initiated. Plasmapheresis or intravenous immunoglobulin may be considered for grade 3 and higher events according to ASCO guidelines, although NCCN only recommends adding on plasmapheresis or intravenous immunoglobulin if there is no improvement or worsening symptoms despite corticosteroids.

Patients with peripheral neuropathy may require a low dose of corticosteroids and immune checkpoint inhibitor therapy should be discontinued. GABA agonists, such as gabapentin and pregabalin, or duloxetine may be considered for peripheral neuropathy. Patients with aseptic meningitis or encephalitis may require a moderate dose of corticosteroids, and empiric antivirals, such as acyclovir, may be started for aseptic meningitis and encephalitis. If patients are confirmed for aseptic meningitis, a low to moderate dose of corticosteroids may be initiated. Patients with transverse myelitis or Guillain-Barre syndrome may require high doses of corticosteroids. Plasmapheresis or intravenous immunoglobulin has been considered for patients with transverse myelitis. Rituximab may be considered for grade 3 and higher, as well as patients positive for autoimmune encephalopathy. Frequent pulmonary function assessment and neurologic evaluation are advised.

Cardiovascular

Cardiovascular irAEs may include myocarditis, pericarditis, arrhythmias, and impaired ventricular function that typically occurs within the first months of treatment. They were initially thought to have a low

incidence rate (< 1%), however, recent evidence suggests that ICI-associated cardiovascular toxicity, myocarditis in particular, is more common than initially thought (NCCN 2024[31]). For all grades of irAEs, immune checkpoint inhibitors should be permanently discontinued, and moderate to high-dose corticosteroids are recommended as treatment. According to NCCN guidelines, infliximab may be considered for life-threatening symptoms. Although myocarditis is extremely rare, it can be fatal, and suspected cases should be admitted for monitoring. If myocarditis is confirmed, high-dose corticosteroids should be administered. Evaluation of cardiovascular irAEs should include chest imaging to rule out pulmonary embolism, pneumonitis, or pulmonary edema. Electrocardiograms should also be monitored closely, and cardiac biomarkers should be tested at baseline and repeated if symptoms arise. A two-dimensional echocardiogram may be considered for patients with significant dyspnea or abnormal cardiac safety screening test result.

Rheumatologic/musculoskeletal

The incidence of musculoskeletal toxicities is 2–12% and can present as inflammatory arthritis, myalgias, myositis, and polymyalgia-like syndromes. Grade 1 patients may continue immune checkpoint inhibitor therapy with the initiation of analgesics (e.g., acetaminophen or nonsteroidal anti-inflammatory drugs). Grade 2 patients should consider holding immune checkpoint inhibitors and starting low-dose corticosteroids for 4–6 weeks. Grade 3–4 patients should permanently discontinue immune checkpoint inhibitors, except for select patients cleared after consultation with a rheumatologist, and moderate dose corticosteroids should be initiated. Infliximab or tocilizumab may be considered for refractory/severe arthritis, and antirheumatic drugs (e.g., sulfasalazine, methotrexate, or leflunamide) may be considered if there is no improvement after 2 weeks (NCCN). Grade 3–4 patients with myositis may be offered plasmapheresis, intravenous immunoglobulin therapy, or immunosuppressant therapy with methotrexate, azathioprine, or mycophenolate mofetil if symptoms do not improve or worsen after 4–6 weeks. Grade 3–4 patients with polymyalgia-like syndrome without improvement from corticosteroids may be offered methotrexate or tocilizumab.[4] Finally, it is important to also consider referring patients with grades 2–4 rheumatological irAEs to a rheumatologist.

Hematologic

Hematologic irAEs are rare and should be supported by changes in laboratory values. The most common adverse effects are hemolytic anemia and thrombocytopenia. Generally, grade 1 patients with hemolytic anemia, ITP, and lymphopenia should continue immune checkpoint inhibitors with continuous monitoring while those with acquired thrombotic thrombocytopenic purpura (TTP), aplastic anemia and acquired hemophilia A should not. Grade 2 patients should hold immune checkpoint inhibitors, and grade 3 or higher patients should permanently discontinue immune checkpoint inhibitors. Grades 1–2 toxicities may be treated with low-dose corticosteroids, while grades 3–4 may require moderate-dose corticosteroids.

For autoimmune hemolytic anemia with no improvement after moderate dose corticosteroid therapy, consider rituximab, intravenous immunoglobulin, cyclosporine A, or mycophenolate mofetil. In acquired thrombotic thrombocytopenic purpura, corticosteroids should be initiated and rituximab may be offered. For hemolytic uremic syndrome, therapy with moderate-dose corticosteroid and eculizumab may be initiated. For lymphopenia, immune checkpoint inhibitors may be continued unless for grade 4, in which case immunotherapy should be held. For thrombocytopenia, discontinue immune checkpoint inhibitors and initiate moderate dose corticosteroids; intravenous immunoglobulin, rituximab, or a thrombopoietin receptor agonist may also be considered. For aplastic anemia and acquired hemophilia, immune checkpoint inhibitors should be permanently discontinued, and patients should be treated with low to moderate doses of corticosteroids, and the addition of rituximab or cyclophosphamide may be considered. Moreover, antithymocyte globulin equine with cyclosporine is an option for aplastic anemia.

Emerging trends to optimize management of irAE

Personalized medicine

Personalized medicine, which includes pharmacogenomics, has the potential to significantly improve the management of irAEs associated with ICI therapy. Pharmacogenomic approaches can identify genetic variants that may influence drug (including immunosuppressants and antibody therapeutics) metabolism, response, and toxicity. For example, genetic polymorphisms in the cytochrome P450 (CYP) 3A4/5 enzyme affect the metabolism of calcineurin inhibitors (cyclosporine A and tacrolimus). These enzymes play a role in drug clearance, and variations can lead to differences in drug levels and efficacy.[43] In addition, polymorphisms in Fc receptors affect clinical response to some antibody therapeutics like rituximab. The knowledge of personalized medicine aids health care practitioners in predicting and managing irAEs more effectively, enhancing patient safety. Furthermore, this approach has the potential to also increase efficacy of ICI therapy through genomic and molecular profiling. Current studies are still ongoing in this area of research; however, some findings have been documented. For example, highly cancer-specific antigens derived from somatic mutations, called neoantigens, can be used to create a unique antigenic profile of a patient's cancer. The immune response to neoantigens can be monitored to assess the effectiveness of ICI therapy and manage irAEs accordingly by tracking T-cell responses to the neoantigens.[44,45] Though more research is still needed in this area, personalized medicine can enable optimized therapeutic outcomes while minimizing the risk of adverse reactions.

Inter-disciplinary teams

Immune checkpoint inhibitors are associated with various irAEs affecting multiple organ systems and may have a delayed presentation. Identification of irAEs includes challenges that can be encountered in the absence of inter-disciplinary collaboration. A pharmacy consult service may help increase the identification of patients with side effects as a result of immune checkpoint inhibitors and initiate timely interventions.[46] In addition, immune checkpoint inhibitors combined with chemotherapy (ICIC) are becoming more widely used for various types of cancers as they are usually more effective than either modality alone. However, ICIC is often associated with an increased incidence of adverse effects. The provision of pharmaceutical care to patients with cancer receiving ICIC therapies can optimize drug therapy and reduce adverse events.[47] Furthermore, immune-related adverse events are complications of immune checkpoint inhibitors which require robust patient education and proactive follow-up to ensure timely identification and management. A recent study[48] evaluated the clinical impact of pharmacist-led, interdisciplinary management and monitoring of patients on ICIs and reported that intensive immune-related adverse event education, proactive follow-up, and immune-related adverse event management by pharmacists resulted in improved patient outcomes and lower odds of treatment discontinuation due to irAEs.

Artificial intelligence tools

The role of technology and artificial intelligence (AI) in managing the adverse effects of ICI therapy is becoming increasingly significant. AI, particularly machine learning models, can predict patient responses to ICIs by analyzing electronic health record (EHR) data. This allows for a personalized approach to treatment by aiding the identification of patients who are likely suitable candidates for ICI therapy and anticipating

potential risks.[49] AI-driven tools can also streamline the management of irAEs by providing health care professionals with guidelines and strategies for diagnosis and treatment. These tools can harmonize irAE management guidelines, standardize reporting, and optimize the choice of immunosuppressive agents. Additionally, they can incorporate diagnostic tools to personalize irAE management using wireless technology and digital health, thus improving patient outcomes.[50] Moreover, AI can assist in conducting preclinical, clinical, and translational studies to better understand irAEs, including those in high-risk patients. By sharing evolving data and incorporating the patient's voice, AI can play a crucial role in enhancing the management of irAEs and advancing precision medicine in oncology.[50] Furthermore, there are applications available to detect irAEs. For instance, "irAE Search" is an easy-to-use application designed to help health care professionals identify potential irAEs in patients treated with ICIs in a timely manner to facilitate prompt management/treatment.[51]

Conclusions

The expanding repertoire of immune checkpoint inhibitors, their clinical applications, and associated adverse effects make it imperative for oncology nurses, and other clinicians involved in the care of cancer patients, to be constantly abreast with current information on the management of irAEs which differ significantly from management of adverse events from cytotoxic chemotherapy. In addition, inter-professional collaboration is strongly recommended amongst health care practitioners to ensure timely identification and management of adverse effects. Understanding the similarities and key differences in the management of irAEs across the available clinical guidelines will facilitate the successful development and implementation of a practice site-specific plan for the management of irAEs. Finally, the use of personalized medicine and AI in the management of adverse effects of ICI should be leveraged.

CRediT authorship contribution statement

Ninh M. La-Beck: conceptualization, writing of original draft, reviewing and editing. Jesuwapelumi Owoso: writing of original draft, reviewing and editing. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethics statement

Not required.

Funding

This work was not externally funded.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

References

1. Dobosz P, Dzieciątkowski T. The intriguing history of cancer immunotherapy. *Front Immunol*. 2019;10:2965.
2. Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. *J Immunol*. 2014;192(12):5451–5458.
3. Fares J, Fares MY, Fares Y. Immune checkpoint inhibitors: Advances and impact in neuro-oncology. *Surg Neurol Int*. 2019;10(1):18–22.
4. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol*. 2016 Feb;39(1):98–106.
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674.
6. Hematology/Oncology (Cancer) Approvals & Safety Notifications. *U.S. Food and Drug Administration*. Maryland: Silver Spring; Dec 2018. Available from https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.
7. Lee N, Zakka LR, Mihm Jr MC, Schatton T. Tumour-infiltrating lymphocytes in melanoma prognosis and cancer immunotherapy. *Pathology*. 2016;48(2):177–187.
8. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. *Cancer Biol Therapy*. 2019;20(11):1366–1379.
9. Chocarro L, Bocanegra A, Blanco E, et al. Cutting-edge: preclinical and clinical development of the first approved Lag-3 inhibitor. *Cells*. 2022 Jul 30;11(15):2351. https://doi.org/10.3390/cells11152351. PMID: 35954196; PMCID: PMC9367598.
10. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: Mechanisms of action, efficacy, and limitations. *Front Oncol*. 2018;8(MAR):1–14.
11. Munn DH, Sharma MD, Johnson TS. Treg Destabilization and Reprogramming: Implications for Cancer Immunotherapy. *Cancer Res*. 2018;78(18):5191–5199.
12. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Therapeut*. 2015;14(4):847–857.
13. Wang X, Teng F, Kong L, Yu J. PD-L1 expression in human cancers and its association with clinical outcomes. *OncoTargets Therapy*. 2016;9:5023–5039.
14. Yervoy (ipilimumab) Package Insert. *Bristol-myers Squibb*; Jul 2018. New York, New York, USA. Available from https://packageinserts.bms.com/pi/pi_yervoy.pdf.
15. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol*. 2016;17(11):1558–1568.
16. Olbryt M, Rajczykowski M, Widłak W. Biological factors behind melanoma response to immune checkpoint inhibitors. *Int J Molecul Sci*. 2020;21(11):1–20.
17. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10):1020–1030.
18. Keytruda (pembrolizumab) Package Insert. *Merck Sharp & Dohme Corp. Whitehouse Station*; Dec 2018. New Jersey, USA. Available from: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.
19. Opdivo (nivolumab) Package Insert. *Bristol-myers Squibb*; Nov 2018. New York, NY, USA. Available from https://packageinserts.bms.com/pi/pi_opdivo.pdf.
20. Libtayo (cemiplimab) Package Insert. *Regeneron Pharmaceuticals, Inc. Tarrytown*; Sept 2018. New York, USA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761097s000lbl.pdf.
21. Tecentriq (atezolizumab) Package Insert. *Genentech*. South San Francisco, California, USA: Inc.; Dec 2018. Available from: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf.
22. Imfinzi (durvalumab) Package Insert. *AstraZeneca Pharmaceuticals LP. Wilmington*. USA: Delaware; Feb 2018. Available from https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1.
23. Bavencio (avelumab) Package Insert. *EMD Serono*. Massachusetts, USA: Inc. Rockland; Oct 2018. Available from: https://www.emdserono.com/content/dam/web/corporate/non-images/country-specifics/us/pi/bavencio-pi.pdf.
24. Long L, Zhang X, Chen F, et al. The promising immune checkpoint LAG-3: from tumor microenvironment to cancer immunotherapy. *Genes Cancer*. 2018;9(5–6):176–189.
25. Lecocq Q, Keyaerts M, Devoogdt N, Breckpot K. The next-generation immune checkpoint LAG-3 and its therapeutic potential in oncology: third time's a charm. *Int J Mol Sci*. 2020;22(1).
26. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022;386(1):24–34.
27. Turnis ME, Korman AJ, Drake CG, Vignali DA. Combinatorial Immunotherapy: PD-1 may not be LAG-ing behind any more. *Oncoimmunology*. 2012;1(7):1172–1174.
28. Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res*. 2012;72(4):917–927.
29. *OPDUALAG™ (nivolumab and relatlimab-rmbw) [package insert]*. Princeton, NJ: Company; 2022.
30. La-Beck NM, Jean GW, Huynh C, Alzghari SK, Lowe DB. Immune checkpoint inhibitors: new insights and current place in cancer therapy. *Pharmacotherapy*. 2015 Oct;35(10):963–976.
31. Management of Immunotherapy-Related Toxicities. National comprehensive cancer Network (NCCN) guidelines. Version 1.2024. Available from: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.
32. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *Erratum. JCO*. 2022;40:315. https://doi.org/10.1200/JCO.21.02786.
33. Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse

events. *J ImmunoThera Cancer*. 2021;9:e002435. https://doi.org/10.1136/jitc-2021-002435.
34. Haanen J, Obeid M, Spain L, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022 Dec;33(12):1217–1238. https://doi.org/10.1016/j.annonc.2022.10.001.
35. Khan M, Lin J, Liao G, et al. Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2018 Aug;97(33):e11936.
36. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018 Jan 11;378(2):158–168.
37. Suijkerbuijk KP, Van Eijs MJ, Van Wijk F, Eggermont AM. Clinical and translational attributes of immune-related adverse events. *Nature Cancer*. 2024:1–15. https://doi.org/10.1038/s43018-024-00730-3.
38. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016 Feb;54:139–148.
39. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. *BMJ*. 2018 14;360:k793.
40. Jamal Shahin, Hudson Marie, Fifi-Mah Aurore, Ye Carrie. Immune-related adverse events associated with cancer immunotherapy: a review for the practicing rheumatologist. *J Rheumatol*. Feb 2020;47(2):166–175. https://doi.org/10.3899/jrheum.190084.
41. Chennamadhavuni A, Abushahin L, Jin N, Presley CJ, Manne A. Risk factors and biomarkers for immune- related adverse events: a practical guide to identifying high-risk patients and rechallenging immune checkpoint inhibitors. *Front Immunol*. 2022;13:779691. https://doi.org/10.3389/fimmu.2022.779691.
42. Common Terminology Criteria for adverse events (CTCAE) | Protocol Development | CTEP [Internet]. [cited 2018 Dec 20]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.
43. Qiu Xy, Wu Z, Xu Qx, Sheng Cc, Jiao Z. Pharmacogenomics of immunosuppressants. In: Cai W, Liu Z, Miao L, Xiang X, eds. *Pharmacogenomics in Precision Medicine*. Singapore: Springer; 2020. https://doi.org/10.1007/978-981-15-3895-7_5.
44. Kiyotani K, Toyoshima Y, Nakamura Y. Personalized immunotherapy in cancer precision medicine. *Cancer Biol Med*. 2021 Aug 9;18(4):955–965. https://doi.org/10.20892/j.issn.2095-3941.2021.0032. Epub ahead of print. PMID: 34369137; PMCID: PMC8610159.
45. Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. *Nat Rev Clin Oncol*. 2021;18(4):215–229. https://doi.org/10.1038/s41571-020-00460-2.
46. Kamta J, Magruder B, Hymel L. Implementation of a pharmacy consult service for evaluation of immune checkpoint inhibitor related adverse events at a large community hospital. *J Oncol Pharm Pract*. 2021 Dec;27(8):1821–1828. https://doi.org/10.1177/1078155220970266. Epub 2020 Nov 11. PMID: 33176559.
47. Kou W, Lin YY, Su F, et al. The influence of pharmaceutical care in patients with advanced non-small-cell lung cancer receiving combination cytotoxic chemotherapy and PD-1/PD-L1 inhibitors. *Front Pharmacol*. 2022 Oct 18;13:910722. https://doi.org/10.3389/fphar.2022.910722. PMID: 36330095; PMCID: PMC9623061.
48. Myers G, Stevens J, Flewelling A, Richard J, London M. Evaluation and clinical impact of a pharmacist-led, interdisciplinary service focusing on education, monitoring and toxicity management of immune checkpoint inhibitors. *J Oncol Pharm Pract*. 2023 Jan;29(1):145–154. https://doi.org/10.1177/10781552211061133. Epub 2021 Nov 30. PMID: 34846197.
49. Lippenszky L, Mittendorf KF, Kiss Z, et al. Prediction of effectiveness and toxicities of immune checkpoint inhibitors using real-world patient data. *JCO Clin Cancer Inform*. 2024;8:e2300207. https://doi.org/10.1200/CCI.23.0020.
50. Naing A, Hajjar J, Gulley JL, et al. Strategies for improving the management of immune-related adverse events. *J ImmunoThera Cancer*. 2020;8:e001754. https://doi.org/10.1136/jitc-2020-001754.
51. Osawa T, Abe T, Kikuchi H, et al. Validation of an online application to identify potential immune-related adverse events associated with immune checkpoint inhibitors based on the patient's symptoms. *PLoS One*. 2022 Mar 15;17(3):e0265230. https://doi.org/10.1371/journal.pone.0265230. PMID: 35290407; PMCID: PMC8923505.