Inhibitors against cytotoxic T-lymphocyte–associated protein 4 and programmed cell death 1 immune checkpoints are novel agents that modulate immune pathways and enhance anti-tumour immunity. Their use has set new standards in the treatment of many cancer types. Some patients with tumours previously deemed incurable are now able to achieve long-term remissions. Immune checkpoint inhibitors are increasingly used, either as stand-alone treatments or in combination with chemotherapy, surgery and radiotherapy, not only for patients with refractory metastatic cancer, but also earlier in the cancer cycle as adjuvant and neoadjuvant treatments. Although these treatments are usually well tolerated, severe and, rarely, fatal adverse events have occurred, especially if not promptly recognized and treated. These reactions, called immune-related adverse events, are the consequence of off-target immune attack on the host's healthy tissues. Given the wide spectrum of sometimes unconventional clinical presentations and response to standard treatments, physicians must maintain a high level of clinical suspicion of immune-related adverse events when managing patients who are treated with immune checkpoint inhibitors. The objective of this review is to provide the general clinician with the necessary tools to recognize, understand and begin management of immune-related adverse events. Our search for the evidence supporting this review is detailed in Box 1.

What are immune checkpoint inhibitors and how do they work?

The idea of exploiting the host immune system to treat cancer relies on the insight that the immune system can eliminate malignant cells in a process termed immune surveillance. During this process, positive and negative immune checkpoints ensure a balance between the hosts' defence against tumour antigens and autoimmunity. Tumour cells can distort some of these signals, allowing the cells to escape immune destruction and progress to cancer. Cytotoxic T-lymphocyte–associated protein 4 and programmed cell death 1 inhibitors are 2 important negative immunomodulatory checkpoints; they are T-cell surface receptors that, when engaged, turn off immune function at different stages of the immunity cycle (Figure 1). Their inhibition thereby allows for ongoing T-cell activation and enhances anti-tumour immunity.

Health Canada's clinical indications for the use of immune checkpoint inhibitors are summarized in Table 1. Because more than a thousand clinical trials are underway assessing different immune checkpoint inhibitors alone or in combination with other standard cancer therapies such as chemotherapy, surgery and radiotherapy, the number of approved indications and patients exposed to these treatments is expected to rise substantially in coming years.

Why do immune-related adverse events occur?

If immune tolerance is defined as a state of unresponsiveness of the immune system toward antigens or tissues able to elicit an immune response, immune-related adverse events represent the other end of the spectrum, where an activated immune system

---

**Key points**

- Immune-related adverse events can occur in any organ at any time during treatment, and possibly after discontinuation of immune checkpoint inhibitors.
- The most important step in managing immune-related adverse events is to recognize them promptly and administer corticosteroids for grade 2 or higher reactions.
- Management of immune-related adverse events is complex, requiring the input of a multidisciplinary team.
- Substantial research is yet to be done on the predictive biomarkers of immune-related adverse events and on their optimal management.
reacts against both tumour antigens and antigens on healthy tissues. This process is tightly regulated by a complex network of cell surface receptors and signalling pathways. By blocking the inhibitory signals, immune checkpoint inhibitors can sway immune responses away from tolerance and in favour of an activated state. Although this is useful for targeting cancer, an immune episode targeted to healthy tissue is also possible. As such, both cytotoxic T-lymphocyte–associated protein 4 and programmed cell death 1 inhibitors have been associated with inflammatory or autoimmune reactions of the human body’s organs (Figure 2). The rates of various immune-related adverse events may differ depending on the particular drug, but the full spectrum of these adverse events can occur with all drugs (Table 2). 

Similarly, although some temporal patterns have emerged for each specific immune-related adverse event, it is important to highlight that any such adverse event can occur at any time during treatment. Some cases of autoimmune disease have been attributed to immune checkpoint inhibitors months after cessation of treatment. Clinicians must be on the lookout for any new symptoms reported by patients who have been exposed to immune checkpoint inhibitors. Early recognition is key, as immune-related adverse events are usually reversible, even when severe in presentation.

Figure 1: A) Antigen presenting cells (APC), such as dendritic cells (DC), scout the human body, sampling different antigens, including tumour-associated antigens, which are then processed and presented through the major histocompatibility (MHC) complex. In a priming phase that takes place in peripheral lymph nodes, APC educate and activate antigen-specific T cells. T cell activation is kept in check by cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), a negative regulator of T-cell function. This negative signal can be blocked by CTLA-4 inhibitors (i.e., ipilimumab), allowing ongoing T-cell activation and migration to the tumour bed. B) Activated T cells also express programmed cell death 1 (PD1), and its ligands, PDL1 and PDL2, are commonly expressed on APC. PD1 and PDL1/PDL2 interaction also inhibits T-cell responses. Tumours can express PDL1 and PDL2 receptors, and engagement of these receptors with the PD1 receptor on T cells turns off T cells and allows tumours to escape destruction. These immune checkpoints can be blocked by PD-1 inhibitors (i.e., nivolumab, pembrolizumab) or PDL-1 inhibitors (i.e., atezolizumab, avelumab and durvalumab). CTLA-4 inhibition results in more widespread and severe immune-related adverse events (irAE), as it regulates T-cell function early in the immunity cycle. Blocking PD-1, on the other hand, is more specific to the tumour microenvironment and, in general, results in less widespread and severe irAE. Note: CD28 = cluster of differentiation 28, TCR = T-cell receptor.

How are immune-related adverse events diagnosed and managed?

We previously reported the case of a patient who developed cerebritis, which rapidly evolved to a profound comatose state after delays in consultation with the treating oncology team and administration of corticosteroids. This example highlights a critical step in the management of immune-related adverse events, which is early recognition and prompt administration of treatment. Patients may present to their primary care physician or to the emergency department outside their routine oncological visits. As such, frontline health care workers may be involved in the initial assessment and management of immune-related adverse events and are encouraged to rapidly consult with the treating oncologists.

Both the American Society of Clinical Oncology and the European Society of Medical Oncology have released comprehensive clinical guidelines on the diagnosis and management of immune-related adverse events. In summary, adverse events are graded according to the Common Terminology Criteria for Adverse Events (Table 3).

Principles of treatment are outlined in Figure 3, which is adapted from the latest American Society of Clinical Oncology guideline. Close observation and symptomatic management without interruption of immune checkpoint inhibitors are recommended for grade 1 reactions.
Table 1: Health Canada–approved indications for immune checkpoint inhibitors in Canada (as of December 2018)*

| Agent | Advanced melanoma | Advanced NSCLC | Advanced RCC | Advanced SCCHN | Advanced bladder cancer | Merkel cell cancer | Hepato-cellular carcinoma | Hodgkin lymphoma |
|-------|-------------------|----------------|--------------|----------------|------------------------|--------------------|--------------------------|------------------|
| CTLA-4 inhibitor | | | | | | | | |
| Ipilimumab | All lines of treatment | | | | | | | |
| PD-1 inhibitors | | | | | | | | |
| Pembrolizumab | 1st-line 2nd-line | 1st-line: (≥ 50% PDL-1+) 2nd-line: (≥ 1% PDL-1+) | | | 2nd-line | Post-autologous stem cell transplant | | |
| Nivolumab | 1st-line 2nd-line | 2nd-line | 2nd-line | 2nd-line | 2nd-line | Post-autologous stem cell transplant | | |
| PDL-1 inhibitor | | | | | | | | |
| Atezolizumab | | 2nd-line | | | 2nd-line | | | |
| Avelumab | | | | | 2nd-line | | | |
| Durvalumab | | | | Post chemotherapy or radiation for stage III disease | | | | |
| Combination (CTLA-4 + PD-1) | | | | | | | | |
| Ipilimumab + nivolumab | 1st-line | 1st-line | | | | | | |

Note: CTLA-4 = cytotoxic T-lymphocyte–associated protein 4, NSCLC = non–small cell lung cancer, PD-1 = programmed cell death 1, PDL-1 = programmed death-ligand 1, RCC = renal cell carcinoma, SCCHN = squamous cell carcinoma of head and neck.

*Health Canada Drug Product Database: www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html (accessed 2018 Dec. 13).

Figure 2: Organs affected by and manifestations of immune-related adverse events.
Oral corticosteroids (0.5–1 mg/kg) are recommended for grade 2 reactions, while treatment with immune checkpoint inhibitors is held. Once a grade 2 reaction has subsided to grade 1 or resolved and steroids have been tapered and stopped, immune checkpoint inhibitors can be resumed at the same dose and schedule.

Grade 3 or higher reactions are managed with high-dose oral or intravenous corticosteroids (prednisone 1 mg/kg or methylprednisolone 2 mg/kg). Intravenous therapy is the preferred route for severe grade ≥ 3 reaction owing to faster onset of action. Patients should be monitored daily until resolution of symptoms, either in hospital or by outpatient visits. Escalation of immunosuppressive treatment is recommended for grade 3 or higher reactions that fail to improve within 48 to 72 hours of high-dose corticosteroid therapy. Tumour necrosis factor inhibitors such as infliximab are preferred as a second-line immunosuppressant. Other drugs that inhibit T cells, including mycophenolate mofetil, have also been used with success. In most cases, grade 3 or higher reactions are considered grounds for permanent discontinuation of immune checkpoint inhibitors. Corticosteroids should be tapered slowly, in most cases no faster than over 4 weeks, as flare-ups are common if immunosuppression is tapered too quickly. As with any immunosuppressive treatment, appropriate prophylaxis against opportunistic infections and monitoring patients for other corticosteroid adverse effects are important.

Endocrine immune-related adverse events (i.e., hypothyroidism, adrenal insufficiency, hypogonadism and hypophysitis) are the only adverse events that do not require permanent discontinuation of immune checkpoint inhibitors, regardless of the severity of the reaction, as long as patients achieve a stable clinical status on physiologic hormonal replacement therapy.

Table 2: Rates of the more common immune-related adverse events stratified by immune checkpoint inhibitor strategy

| Immune-related adverse events | Anti–CTLA-4 (ipilimumab) | Anti–PD-1 (nivolumab) | Anti–CTLA4 + Anti–PD1 (ipilimumab + nivolumab) |
|------------------------------|--------------------------|-----------------------|-----------------------------------------------|
|                              | Any grade, % | Grade ≥ 3, † % | Any grade, % | Grade ≥ 3, † % | Any grade, % | Grade ≥ 3, † % |
| All immune-related adverse events | 86          | 27            | 82          | 16            | 96          | 55            |
| Rash                         | 33          | 2             | 26          | 1             | 40          | 5             |
| Colitis                      | 12          | 9             | 1           | 1             | 12          | 8             |
| Diarrhea                     | 33          | 6             | 20          | 2             | 44          | 10            |
| Hepatitis                    | 4           | 2             | 4           | 1             | 18          | 8             |
| Hypothyroidism               | 4           | 0             | 9           | 0             | 15          | 1             |
| Discontinuation owing to immune-related adverse events | 15 | 13 | 8 | 5 | 36 | 30 |

Note: CTLA-4 = cytotoxic T-lymphocyte–associated protein 4, irAE = immune-related adverse events, PD-1 = programmed cell death 1.

*Results are based on a large phase 3 clinical trial comparing the efficacy and safety of single-agent PD-1, CTLA-4 or the combination in metastatic melanoma. Similar immune-related adverse events rates are reproducible in other cancer types.

†Grade 3 = severe or medically important but not immediately life-threatening; hospital admission indicated; disabling; limiting self-care, per Common Terminology Criteria for Adverse Events.

Table 3: General grading guidelines from the Common Terminology Criteria for Adverse Events

| CTCAE grade | Description |
|-------------|-------------|
| 1           | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2           | Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activity of daily living. |
| 3           | Severe or medically significant but not immediately life-threatening; hospitalization indicated; disabling; limiting self care. |
| 4           | Life-threatening consequences; urgent intervention indicated. |
| 5           | Death related to adverse event. |

Note: CTCAE = Common Terminology Criteria for Adverse Events. CTCAE provides general grading guidelines as described within this table. For each specific organ affected, the CTCAE also provides descriptive organ-specific grading.
≥ 3 reactions, prompt high-dose intravenous corticosteroid therapy should not be delayed in favour of other investigations. Invasive diagnostic tests and confirmatory biopsies are often challenging to obtain and can lead to complications or delays in treatment. For instance, diagnostic colonoscopies in the setting of colitis from immune checkpoint inhibitors could induce bowel perforation, and should not be routinely performed.13

What is the impact of immune-related adverse events on cancer outcomes?

Early clinical observations suggested that patients with severe immune-related adverse events seemed to derive greater anti-tumour benefit, sometimes lasting long after the immune checkpoint inhibitors were permanently discontinued. Thus, the occurrence of immune-related adverse events was thought to be tangible proof that the patient’s immune system was activated. Whether this immunological activation correlates with improved cancer outcomes remains controversial. For instance, in one large, retrospective study, cancer outcomes were similar in patients with melanoma who were treated with both ipilimumab and nivolumab, serious toxicities leading to early discontinuation have been associated with good overall survival.16 In 2 recent series, the development of immune-related adverse events in patients with lung cancer who were undergoing therapy with immune checkpoint inhibitors was associated with improved survival.17,18 In summary, the current consensus is that immune-related adverse events are not required to obtain a benefit from immune checkpoint inhibitors, but their occurrence is potentially associated with improved cancer-related outcomes in some settings. Further research and large-scale cohort studies are required to investigate this association.

Are immune checkpoint inhibitors suitable for patients with pre-existing autoimmune diseases?

Patients with autoimmune diseases have been excluded from clinical trials investigating immune checkpoint inhibitors owing to concerns regarding disease flare-ups. In the real-life clinical setting, clinicians have offered immune checkpoint inhibitors to these patients, based on the assumption that the benefits may outweigh the risks. There is some, albeit limited, evidence to support this. These patients seem to derive the same amount of clinical benefit from immune checkpoint inhibitors as the standard populations in which these therapies were studied.19-21

---

**Figure 3:** Summarized management strategies for immune-related adverse events (irAE), adapted from the latest American Society of Clinical Oncology (ASCO) guideline.10 The only exception to this algorithm is the management of endocrine irAE, where physiologic hormone replacement, rather than high-dose steroid use, is recommended for any grade irAE. *High-dose steroids, defined as 1 mg/kg, or oral prednisone or 2 mg/kg of intravenous solutedrol. Note: CTCAE = Common Terminology Criteria for Adverse Events, ESMO = European Society for Medical Oncology, ICI = immune checkpoint inhibitors.*
far as the autoimmune outcomes are concerned, a systematic review concluded that flare-ups and immune-related adverse events in patients with autoimmune disease on immune checkpoint inhibitors can often be managed without discontinuing therapy, although some events may be severe and fatal.\(^2^\) The optimal immunosuppressive regimen necessary to maintain quiescence of pre-existing autoimmunity without compromising the clinical benefits of immunotherapies has yet to be elucidated. As an example, certain immunomodulatory regimens could be associated with a loss of clinical benefit of immune checkpoint inhibitors.\(^2^\)

The management of patients who have cancer and pre-existing autoimmune diseases and who are receiving immune checkpoint inhibitors is complex and requires a multidisciplinary approach that incorporates oncologists and organ-specific experts, including rheumatologists, gastroenterologists, endocrinologists and dermatologists.

**Can we predict which patients will develop immune-related adverse events?**

There are large gaps in the epidemiology of immune-related adverse events. Demographic risk factors for the development of these events are unknown, including whether female sex, which is a strong risk factor for autoimmunity, is also a risk factor for immune-related adverse events. Although the gut microbiome has been linked to the development of immune checkpoint inhibitor–induced colitis and an intriguing association between response to these inhibitors and gut microbiome has been described,\(^2^\)-\(^6^\) associations between the microbiome outside the gut and immune-related adverse events remain unexplored. The molecular mechanisms underlying immune-related adverse events, and whether they are similar or not to those underlying “classic” autoimmune diseases, are also largely unknown. Genetic susceptibilities, particularly major histocompatibility complex haplotypes, are mostly absent from current analyses for immune-related adverse events.\(^2^\) Cytoxic T-lymphocyte–associated protein 4 polymorphisms have been linked to an increased risk of autoimmune diseases and programmed cell death 1 polymorphisms to autoimmune colitis; mice lacking programmed cell death 1 develop lupus-like syndrome.\(^2^\)\(^3^\)\(^-\)\(^6^\) To date, only limited lupus nephritis, rather than full systemic lupus syndrome, has been reported with the use of immune checkpoint inhibitors.\(^2^\)\(^3^\) As such, the effect of genetic variants of cytoxic T-lymphocyte–associated protein 4, programmed cell death 1, and programmed death-ligand 1 on the risk or severity of immune-related adverse events is unknown. Autoantibodies have been reported in some cases of type 1 diabetes, thyroid disease and arthritis secondary to immune checkpoint inhibitors.\(^2^\)\(^3^\)\(^-\)\(^6^\) Whether these antibodies represent a pre-existing immune diathesis or are the consequence of de novo immunological events remains unknown. Few clinical predictors of immune-related adverse events have been identified, including pre-treatment lymphopenia.\(^3^\)\(^7^\)\(^-\)\(^8^\) Although immune biomarkers predictive of the outcome of treatment with immune checkpoint inhibitors are the object of considerable research, there is a paucity of research on immune biomarkers predicting immune-related adverse events. Unanswered questions are summarized in Box 2.

**References**

1. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015;33:1889-94.
2. Gettinger S, Horn L, Jackman D, et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. J Clin Oncol 2018;36:1675-84.
3. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity’s roles in cancer suppression and promotion. Science 2011;331:1565-70.
4. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
5. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350-5.
6. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.
7. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. PLoS One 2016;11:e0160221.
8. Sznol M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. J Clin Oncol 2017;35:3815-22.
9. Desforges P, Esfahani K, Bouganim N. Programmed cell death ligand 1-induced coma from diffuse cerebritis. J Oncol Pract 2018;14:134-5.
10. Brahmer JR, Lacchetti C, Schneider BJ, et al. 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 2018;36:1714-68.
Correlation between immune-related adverse events and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol 2015;33:3193-8.

- Shoushtari AN, Friedman CF, Navid-Azarbaijani P, et al. Measuring toxic effects and time to treatment failure for nivolumab plus ipilimumab in melanoma. JAMA Oncol 2018;4:98-101.

- Haratani K, Hayashi H, Chiba Y, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol 2017;153:806-12.

- Abdel-Wahab N, Shah M, Lopez-Olivo MA, et al. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 1999;11:141-51.

- Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet 2015;47:979-86.

- Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody-induced lupus nephritis. N Engl J Med 2009;361:211-2.

- Godwin JL, Jaggi S, Sirisena I, et al. Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer. J Immunother Cancer 2017;5:40.

- Oserio JC, Ni A, Chaft JE, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol 2017;28:583-9.

- Belkhir R, Burel SL, Dunogean L, et al. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. Ann Rheum Dis 2017;76:1747-50.

- Diehl A, Yarchan A, Hopkins A, et al. Relationships between lymphocyte counts and treatment-related toxicities and clinical responses in patients with solid tumors treated with PD-1 checkpoint inhibitors. Oncotarget 2017;8:114268-80.

- Suh KJ, Kim SH, Kim YJ, et al. Post-treatment neutrophil-to-lymphocyte ratio at week 6 is prognostic in patients with advanced non-small cell lung cancers treated with anti-PD-1 antibody. Cancer Immunol Immunother 2018;67:459-70.