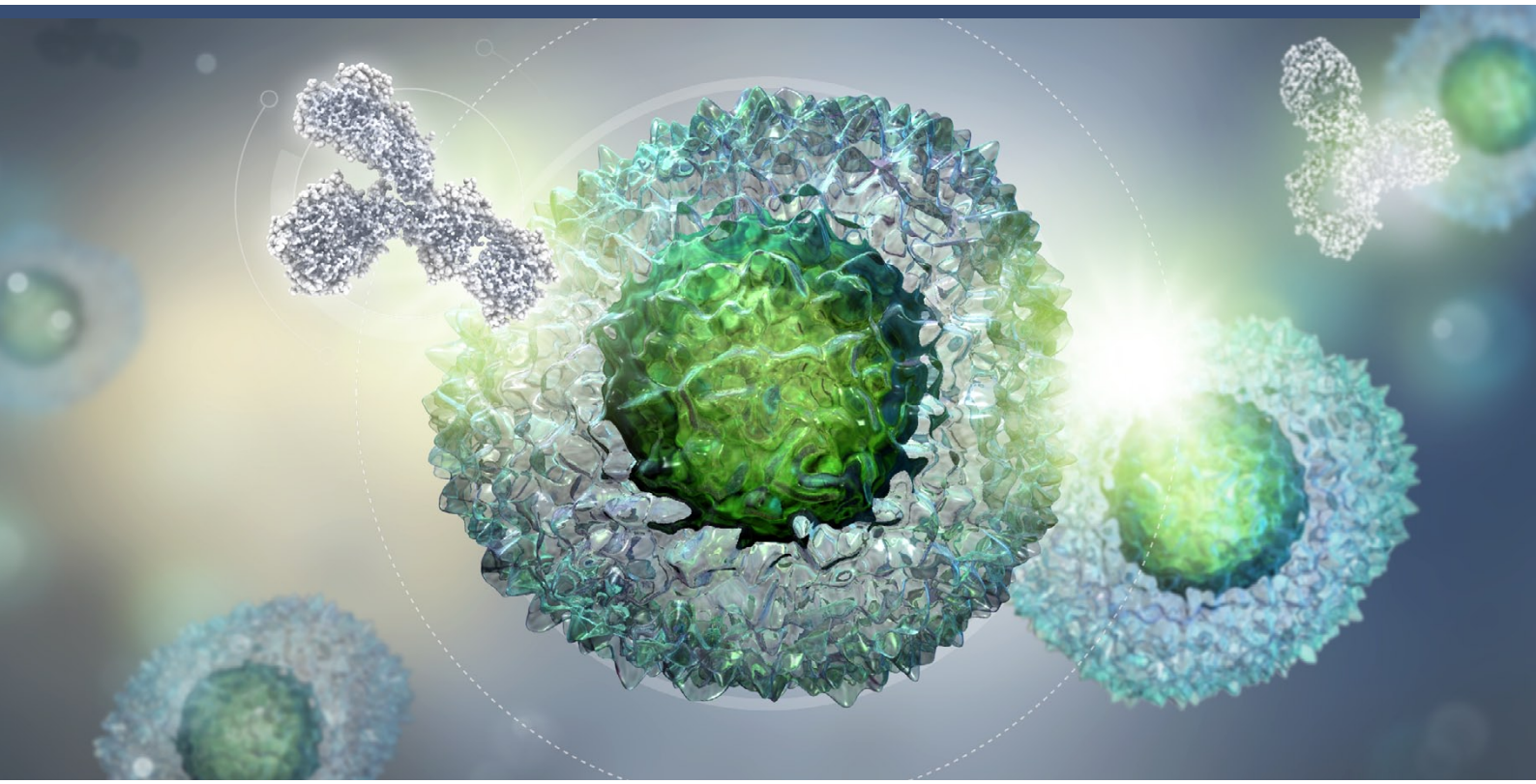

Immune checkpoint inhibitors: a new cancer treatment

Immune checkpoint inhibitors, such as pembrolizumab (Keytruda), are new cancer treatments which are associated with a wide range of immune-related adverse effects. These mostly occur during treatment but can occur months to years after treatment starts. Clinicians in primary care need to be aware of the potential for these adverse effects, in order for patients to receive appropriate diagnosis and management, in liaison with the patient's oncologist.

KEY PRACTICE POINTS:

- Immune checkpoint inhibitors, including pembrolizumab (Keytruda), nivolumab (Opdivo), ipilimumab (Yervoy) and atezolizumab (Tecentriq) are indicated for patients with advanced, metastatic or refractory cancer. These medicines are currently primarily used in patients with melanoma in New Zealand, but may be used for other types of cancer.
- As immune checkpoint inhibitors are new treatments for cancer, the incidence and management of adverse effects from these medicines is an evolving area of clinical practice
- Immune-related adverse effects such as rash, colitis or hypothyroidism can occur at any time, even months after the medicine has been stopped, therefore patients will need to be monitored for symptoms and signs in primary care
- If immune-related adverse effects occur, the patient's treating oncologist should be informed
- Patients may require corticosteroids or hormone substitution treatment to assist with the management of adverse effects of immune checkpoint inhibitors

What are immune checkpoint inhibitors?

Immune checkpoint inhibitors increase T-cell activity against tumour cells, but they also increase T-cell activity against healthy cells

Cancer immunotherapies aim to improve the ability of the body to generate an immune response to tumour cells.[1] Two key receptor systems involved in influencing T-cells and their ability to recognise and target tumours are the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor, and the programmed death-1 (PD-1) receptor and its ligand PD-L1. These two receptor systems act as self-recognition signals to distinguish between cells of the body and foreign pathogens; they are also known as immune checkpoints. Immune checkpoints can be co-opted by tumour cells to reduce T-cell activity and reduce immune responses to cancer.[2] Immune checkpoint inhibitors are antibodies which target these receptor systems and increase T-cell activity in order to improve the immune response to

tumour cells. However, this also results in increased T-cell activity against healthy cells and an increased risk of immune-related adverse effects.

There are currently four immune checkpoint inhibitors approved for use in New Zealand

Immune checkpoint inhibitors approved in New Zealand are currently indicated for use in patients with melanoma, non-small cell lung cancer, renal cancer, bladder cancer and Hodgkin's lymphoma.[3] However, further clinical trials are ongoing and their scope of use in clinical practice is likely to expand to other types of cancer in the future. Some patients in New Zealand may be administered these medicines in clinical trials.

Immune checkpoint inhibitors currently approved for use in New Zealand are:[3, 4]

- Pembrolizumab (Keytruda) and nivolumab (Opdivo), which target the PD-1 receptor; these are subsidised with Special Authority approval for the treatment of inoperable or metastatic melanoma
- Ipilimumab (Yervoy), which targets CTLA-4; it is not subsidised.
- Atezolizumab (Tecentriq), which targets PD-L1, the ligand for the PD-1 receptor; it is not subsidised

Immune checkpoint inhibitors cause immune-related adverse effects, which can occur after treatment has concluded

Patients are treated with immune checkpoint inhibitors for varying lengths of time; they could be treated until their cancer has progressed and they are discharged to home or palliative care, they may have their cancer successfully treated and go into remission with increasing intervals between follow-up appointments, or they may have treatment with an immune checkpoint inhibitor stopped prematurely due to adverse effects.

There are a large range of immune-related adverse effects associated with the use of immune checkpoint inhibitors. Most cases occur within weeks to months of a patient starting treatment, but adverse effects are still possible a year or more later.[5, 6]

Immune-related adverse effects are very common

Many patients administered an immune checkpoint inhibitor will experience some degree of immune-related adverse effect. The most common adverse effects include skin rash, diarrhoea and colitis, thyroiditis and hepatitis. Adverse effects can range from mild to serious in severity, and some rare adverse effects can be potentially fatal. Rare adverse effects are wide ranging and include primary adrenal insufficiency (Addison's disease), colon perforation associated with enterocolitis, type 1 diabetes, renal, cardiac or ocular toxicity and drug rash with eosinophilia and systemic symptoms (DRESS).[7] Table 1 lists the main adverse effects of immune checkpoint inhibitors, and their approximate incidence rate.

Medicines which target CTLA-4, such as ipilimumab, are associated with a greater incidence and severity of adverse effects than medicines which target PD-1 or PD-L1, such as nivolumab, pembrolizumab and atezolizumab.[8]

Meta-analyses of clinical trials show that:[9, 10]

- 27% of patients treated with PD-1/PD-L1 inhibitors develop some degree of immune-related adverse effects, with 6% being severe
- 72% of patients treated with CTLA-4 inhibitors develop some degree of immune-related adverse effects, with 24% being severe

The risk of immune-related adverse effects is higher if combination treatment with both CTLA-4 and PD-1/PD-L1 inhibitors is used than either medicine alone.[7] There are less data available on the incidence of immune-related adverse effects when these medicines are used sequentially. Anecdotal reports suggest a longer duration of treatment with an immune checkpoint inhibitor may be associated with a greater incidence of immune-related adverse effects.

Detecting and managing immune-related adverse effects

Communication between the primary care team and the patient's oncologist is necessary to ensure that potential immune-related adverse effects are detected early and appropriately treated.

If adverse effects occur while the patient is still undergoing treatment, it is likely they will be detected and managed by the oncology team. Management may involve delaying the next dose or withdrawing the immune checkpoint inhibitor.[7] High dose oral corticosteroids are often used to treat the adverse effects, and other medicines may also be necessary (see below).

Consider immune-related adverse effects in patients with unexplained symptoms and signs discovered in primary care

If a patient has received treatment with an immune checkpoint inhibitor, or they are still actively undergoing treatment, clinicians in primary care should be alert for symptoms and signs that may indicate an immune-related adverse effect. If there is suspicion of this, the patient's oncologist should be contacted to discuss an appropriate management strategy.

The symptoms and signs of immune-related adverse effects can be diverse and are often non-specific. As these adverse effects are induced by a medicine, rather than by an autoimmune condition, the speed of onset and severity of symptoms and signs may differ from a general practitioner's

previous experience. Consider if there are any alternative explanations for the signs and symptoms, such as infection, an adverse effect of another medicine or an unrelated condition. Laboratory investigations, such as a full blood count, liver and renal function tests may assist in diagnosis.[7]

Corticosteroids are the cornerstone of treatment

High dose oral corticosteroids, e.g. prednisone 1–2 mg/kg/day, are used to provide immunosuppression while a patient is undergoing treatment with an immune checkpoint inhibitor.[11] Lower doses may be used in patients with less severe symptoms.[7] The aim of corticosteroid treatment is to minimise adverse effects while still allowing sufficient immune response to the cancer being treated. Corticosteroids are also used as a treatment for specific immune adverse effects that may develop, such as low levels of cortisol caused by hypophysitis or primary adrenal insufficiency.[7]

Depending on the organs affected and severity of symptoms, patients may be initiated on a variety of additional treatments in secondary care, such as thyroxine for hypothyroidism, and less commonly infliximab for gastrointestinal adverse effects or mycophenolate mofetil or tacrolimus for severe symptoms or where stronger immunosuppression is required.[7] If patients develop hormone deficiencies due to immune-related adverse effects, they may require hormone substitution for the remainder of their life to replace thyroid, adrenal, pancreatic or sex hormones.

If patients have been initiated on high dose oral corticosteroids, check the intended duration and purpose of treatment

Some patients who have received treatment with an immune checkpoint inhibitor may still be required to take high dose oral corticosteroids after their treatment has concluded. Clinicians in primary care will need to check the patient's notes or instructions from their oncologist regarding the purpose for prescribing oral corticosteroids and the expected length of treatment; the appropriate course of action if patients develop symptoms or signs of adrenal insufficiency will differ depending on the reason for initiation.

If oral corticosteroids were initiated for primary adrenal insufficiency, patients will need to continue them indefinitely and dose increases may be required if symptoms of adrenal insufficiency develop. In other cases, patients may be able to withdraw from oral corticosteroids, with tapering, after an immune-related adverse effect has subsided; this should be done in consultation with the treating oncologist.

Treatment with immune checkpoint inhibitors can affect other aspects of healthcare

Immune-related adverse effects or the treatments initiated to control them, such as high dose corticosteroids, may complicate the management of a patient's general medical conditions. Be alert for the potential for medicine interactions and treatment contraindications or restrictions, such as administering live vaccinations.

Patient information on immune checkpoint inhibitors and their adverse effects is available from: **www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types/checkpoint-inhibitors**

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www.bpac.org.nz/2018/checkpoint.aspx

Table 1. Immune-related adverse effects associated with the use of immune checkpoint inhibitors.[7, 9, 10, 12]

Organ and adverse effect	Approximate incidence rate		Characteristics	Typical timing after treatment starts*
	Patients treated with **PD-1/PD-L1 inhibitors** (e.g. nivolumab, pembrolizumab, atezolizumab)	Patients treated with **CTLA-4 inhibitors** (e.g. ipilimumab)		
Skin	>30%	>30%	Most commonly rash or pruritus. Can include lichenoid drug eruption and vitiligo. Severe cases are rare but can include: ▪ Acute febrile neutrophilic dermatosis (Sweet syndrome) ▪ Stevens-Johnson syndrome ▪ Toxic epidermal necrolysis	Within the first few weeks
Gastrointestinal adverse effects	Between 5–15%	>30%	Can include: ▪ Diarrhoea ▪ Abdominal pain ▪ Weight loss ▪ Fever ▪ Vomiting ▪ Mouth ulcers ▪ Anal lesions ▪ Colon perforation can occur in severe cases	Can occur at any time during treatment. May occur up to several months after the last dose.
Thyroid dysfunction	Between 5–15%	Between 5–15%	Usually hypothyroidism but can present as temporary hyperthyroidism which progresses to hypothyroidism	Two to three months
Immune-related hepatitis	Between 5–15%	Between 5–15%	Hepatitis is usually asymptomatic and detected only on laboratory investigations; monitoring occurs during treatment	One to four months

Hypophysitis (inflammation of the pituitary)	Rare	Between 5–15%	■ Mostly affects males ■ Symptoms include headache, visual disturbances, nausea or symptoms related to hypogonadism and hypothyroidism, e.g. fatigue, weakness, temperature intolerance, insomnia, loss of libido ■ Laboratory investigations may show simultaneously low levels of: – Thyroid stimulating hormone (TSH) – Adrenocorticotropic hormone (ACTH) – Follicle-stimulating hormone (FSH) – Luteinizing hormone (LH) – Cortisol – Testosterone ■ In severe cases may cause life-threatening adrenal insufficiency	Four to five months
Neurological adverse effects	< 5%	< 5%	Can include: ■ Polyneuropathy ■ Facial nerve palsy ■ Myasthenia gravis ■ Guillain-Barré syndrome	One to three months
Pneumonitis	< 5%	< 5%	N.B. Less severe lung adverse effects such as cough and dyspnoea occur in 20-40% of patients administered PD-1/PD-L1 inhibitor treatment (nivolumab, pembrolizumab and atezolizumab)	Four to eight months
Drug rash with eosinophilia and systemic symptoms (DRESS)	Rare	Rare	Assess vital signs, skin surfaces and mucus membranes; lymphadenopathy, facial or distal extremity swelling may indicate DRESS	Rare; no typical timing

* Note that patients may develop late adverse effects occurring a year or more after the start of treatment.[6]