Medicines Adverse Reactions Committee

Meeting date	**14 September 2017**	Agenda item	3.2.2
Title	**Review of Immune Checkpoint Inhibitors in the New Zealand context**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Atezolizumab	Tecentriq	Roche Products (NZ) Ltd
Ipilimumab	Yervoy*	Bristol-Myers Squibb
Nivolumab	Opdivo	Bristol-Myers Squibb
Pembrolizumab	Keytruda	Merck Sharp & Dohme

*This is the brand available in New Zealand at 21 August 2017.

Funding	Opdivo and Keytruda are funded by PHARMAC on the Hospital Medicines List.
Previous MARC meetings	Atezolizumab, ipilimumab, nivolumab and pembrolizumab have not been discussed previously.
Prescriber Update	At 21 August 2017, no *Prescriber Update* articles had been written on immune checkpoint inhibitors.
Schedule	Prescription medicine
Advice sought	**The Committee is asked to advise whether:** – communication to healthcare professionals or consumers other than MARC's Remarks in Prescriber Update is required – any other regulatory actions are required.

Table of Contents

1.0 PURPOSE

Recently Medsafe was informed by the Centre for Adverse Reactions Monitoring (CARM) of two reports of the development of diabetes (Type 1) in patients who had received treatment with pembrolizumab (see section 3.3).

Pembrolizumab, ipilimumab, nivolumab and atezolizumab are medicines called immune checkpoint inhibitors. Given that these medicines are relatively new to New Zealand, their use is anticipated to increase and noting the severity of the recent reports of diabetes received, Medsafe considers a review of these medicines in the New Zealand context should be carried out.

The purpose of this paper is to present current data on the use of pembrolizumab, ipilimumab, nivolumab and atezolizumab.

2.0 BACKGROUND

2.1 Cancer

The availability of cancer medicines in New Zealand is important as cancer is New Zealand's single biggest cause of death [1]. As the population ages more people are developing cancer [1].

Cancer is an uncontrolled growth of body cells. It arises from damage to some of a person's genes, particularly those involved in controlled growth [2]. When cells duplicate themselves instead of undergoing the normal process of growing, dividing, renewing and death, a tumour may develop [2]. Benign tumour cells stay in one place in the body and malignant tumour cells spread into or invade nearby tissues. Malignant tumours may also metastasise (travel) to other parts of the body [2].

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers and lung cancer remains a leading cause of cancer mortality worldwide [3].

There are a number of options for treating cancer which depend on an individual's characteristics such as age and also on the type of cancer and its location [2]. Cancer treatments include surgery, chemotherapy, hormone treatment, radiation treatment and more recently treatment with monoclonal antibodies (see section 2.3), which are the focus of this review [2].

2.2 Immune checkpoints

Stimulatory and inhibitory pathways regulate the inflammatory immune response to protect healthy tissues from damage [4]. Immune checkpoints are inhibitory pathways that reduce the likelihood of an immune attack against normal tissues by down-regulating T cell activation [5, 6]. These checkpoints are crucial in immune responses and are therefore essential for the body to prevent autoimmunity and to protect tissues from damage during infection [6, 7].

Cancer cells must develop immune resistance mechanisms to avoid recognition by the host immune system that allows them to grow [6, 7]. One mechanism used by cancer cells involves immune-inhibitory pathways or immune checkpoints [6]. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two important immune-checkpoint receptors involved in the immune process [6]. These are both inhibitory receptors that use different mechanisms to regulate immune responses [6]. Based on the clinical activity of antibodies that block these receptors it is implied that anti-tumour immunity can be enhanced at multiple levels [6].

2.3 Immune checkpoint inhibitors

Atezolizumab (Tecentriq), ipilimumab (Yervoy), nivolumab (Opdivo) and pembrolizumab (Keytruda) are monoclonal antibodies called immune checkpoint inhibitors [7]. These medicines are used to treat metastatic melanoma and non-small cell lung cancer [8-11].

Immune checkpoint inhibitors target proteins ('checkpoints') on immune cells called T-cells [7]. By blocking these checkpoints, they allow the immune system to boost the immune response against cancer cells [7, 12].

The National Cancer Institute defines 'Immune checkpoint inhibitor' as [12]:

- A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. These proteins help keep immune responses in check and can keep T cells from killing cancer cells. When these proteins are blocked, the 'brakes' on the immune system are released and T cells are able to kill cancer cells better. PD-1 and CTLA-4 are examples of checkpoint proteins found on T cells or cancer cells.

Comments
Medsafe has received applications for extensions of indication and therefore use will increase this way as well.

2.3.1 Immune checkpoint inhibition

2.3.1.1 T-cell activation

The activation and function of T-cells in cell-mediated tumour immunity is controlled through a balance of stimulatory and inhibitory signals [13].

T-cells have an essential role in the immune evasive measures used by cancer cells and also in preventing autoimmunity [3].

Regulatory T-cells suppress cytotoxic (CD8+) T-cells to reduce T-cell-mediated cytotoxic killing [3]. In addition to regulation by regulatory T-cells, T-cell activation involves a balance between co-stimulatory and co-inhibitory (i.e. immune checkpoints) signals [3]. These signals are exchanged during the binding of the T-cell receptor to the major histocompatibility complex (MHC) or to antigen presenting cells (APCs) [3].

T-cell activation requires two signals. Firstly, antigens on the antigen-presenting cells bind with T-cell receptors [14]. Secondly, B7 molecules on the antigen-presenting cell surface bind with CD28 receptors on the T-cell [14]. This second step produces T-cell activation from T-cell receptor stimulation [14]. This process initiates changes such as T-cell proliferation to trigger and amplify the immune process [15].

PD-1 and CTLA-4 are expressed on T-cells when T-cells are activated [5, 14]. Immune checkpoints (including CTLA-4 and PD-1) negatively regulate proliferative and functional consequences of T-cell activation [13].

2.3.2 Medicines that target CTLA-4

T-cell expression of the inhibitory molecule CTLA-4 occurs following T-cell activation [14]. CTLA-4 is expressed exclusively on T-cells and regulates the immune response early [4, 6].

CTLA-4 primarily counteracts the activity of the T-cell co-stimulatory receptor CD28 by competitively inhibiting the binding of B7 to CD28 [6, 14]. By doing this, CTLA-4 dampens T-cell activation and proliferation, decreasing the immune response [14, 15]. CTLA-4 is an important immune checkpoint to prevent unwanted autoimmunity [15].

Ipilimumab (brand name Yervoy) is a monoclonal antibody that binds to CTLA-4 on T cells. Ipilimumab was a first-in-class agent that increased overall survival in metastatic melanoma providing proof that targeting an immune checkpoint can improve outcomes in patients with cancer [13]. This immune checkpoint inhibitor blocks the inhibitory CTLA-4 signal, which in turns results in an intensification of T-cell activation and proliferation, and increases an anti-tumour T-cell immune

response [15, 16]. This creates a T-cell immune attack against tumour cells [9]. This is demonstrated in Figure 1 below, which has been taken from Tarhini et al [15].

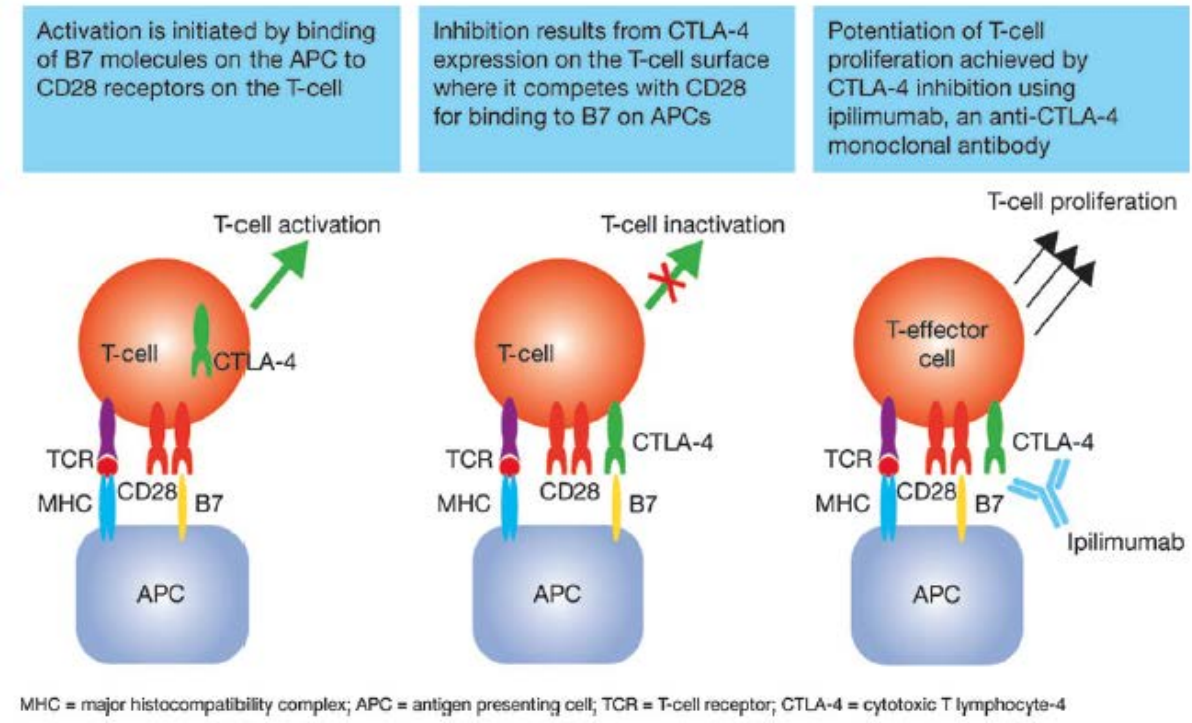


Figure 1 T-cell activation and mechanism of action of ipilimumab. APC – antigen presenting cell, CTLA-4 – cytotoxic T lymphocyte antigen-4, TCR – T-cell receptor, MHC – major histocompatibility complex [15]

Ipilimumab is the currently available medicine in New Zealand that targets CTLA-4. Yervoy (ipilimumab) was approved for use in New Zealand in March 2012, but is not currently funded by PHARMAC. Yervoy is indicated for the treatment of patients with unresectable or metastatic melanoma [9].

2.3.3 Medicines that target PD-1

PD-1 is a checkpoint molecule that is expressed by activated T-cells following chronic infections or tumours [4, 5]. PD-1 is thought to act primarily in peripheral tissues where it limits T-cell activity during an inflammatory response to infection limiting auto-immunity [5, 6]. In contrast to the early acting CTLA-4, PD-1 is thought to affect the T-cell response at a later stage [4]. The major role of PD-1 is to limit the activity of T-cells in peripheral tissues at the time of an inflammatory response to infection rather than at the initial T-cell activation stage [6].

As seen in the figure below, when PD-1 binds to its ligand (PD-L1) the T-cell receives an inhibitory signal which in turn blocks the anti-tumour immune response [4].

Antibodies that target PD-1 will inhibit binding of PD-1 to both its ligands (PD-L1 and PD-L2) with the aim of blocking the PD-1 pathway so anti-tumour immune responses can be restored [4, 5] (Figure 2 [6]).

Nivolumab and pembrolizumab are the medicines currently available in New Zealand that target PD-1.

Nivolumab is a monoclonal antibody which binds to the PD-1 receptor blocking its interaction with PD-L1 and PD-L2 [8]. Through blocking the binding of PD-1 to the ligands PD-L1 and PD-L2, nivolumab potentiates T-cell responses [8] (Figure 2b).

Similarly, pembrolizumab is a monoclonal antibody which reactivates tumour-specific cytotoxic T lymphocytes and reactivates anti-tumour immunity by blocking the PD-1 pathway (including PD-L1 and PD-L2) on antigen-presenting or tumour cells [10] (Figure 2b).

Opdivo (nivolumab) has been approved for use since April 2016 and Keytruda (pembrolizumab) has been approved since September 2015. Both these medicines are currently funded by PHARMAC.

Immune checkpoints regulate different parts in the immune response process. CTLA-4 predominantly regulates T-cell activation and PD-1 predominantly regulates T cell activity within tissue and tumours [6]. This is demonstrated in the following figure and wording which have been taken from Pardoll 2012 [6].

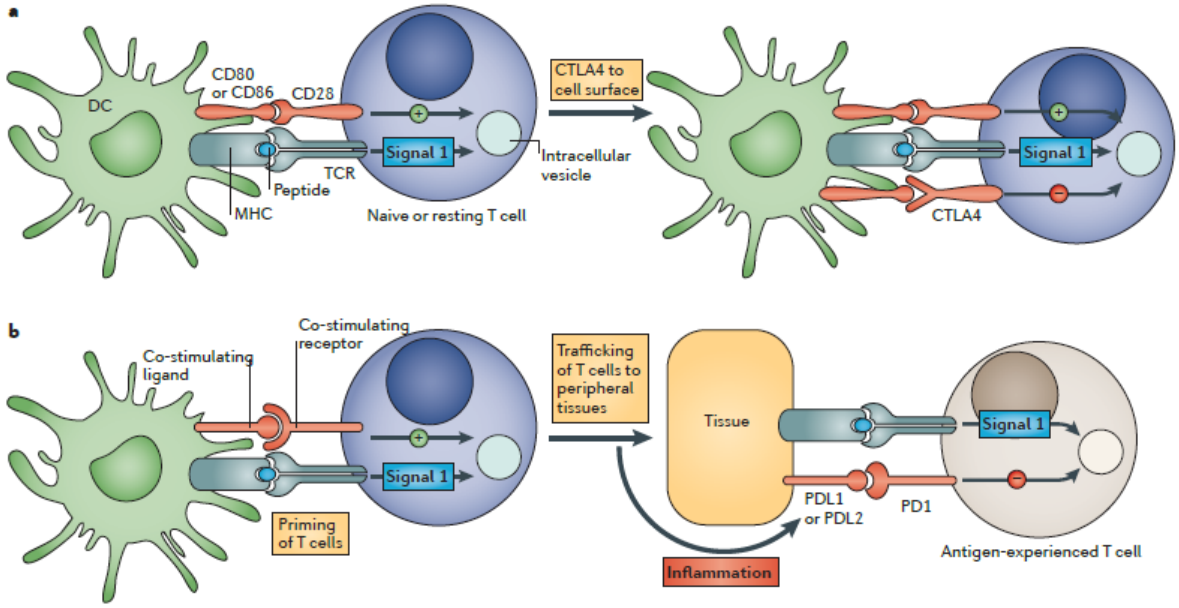


Figure 2 Immune checkpoints regulate different components in the evolution of an immune response [6].

- **a) The CTLA-4-mediated immune checkpoint is induced in T cells at the time of their initial response to antigen. The level of CTLA-4 induction depends on the amplitude of the initial T cell receptor (TCR)-mediated signalling. High affinity ligands induce higher levels of CTLA-4, which dampens the amplitude of the initial response. The key to the regulation of T cell activation levels by the CD28-CTLA-4 system is the timing of surface expression. Naïve and memory T cells express high levels of cell surface CD28 but do not express CTLA-4 on their surface. Instead, CTLA-4 is sequestered in intracellular vesicles. After the TCR is triggered by antigen encounter, CTLA-4 is transported to the cell surface. The stronger the stimulation through the TCR (and CD28), the greater the amount of CTLA-4 that is deposited on the T cell surface. Therefore, CTLA-4 functions as a signal dampener to maintain a consistent level of T cell activation in the face of widely varying concentration and affinities of ligand for the TCR.**
- **b) By contrast the major role of the PD-1 pathway is not at the initial T cell activation stage but rather to regulate inflammatory responses in tissues by effector T cells recognising antigen in peripheral tissues. Activated T cells up-regulate PD1 and continue to express it in tissues. Inflammatory signals in the tissues induce the expression of PD1 ligands, which down-regulate the activity of T cells and this limits collateral tissues damage in response to a microorganism infection in that tissue. The best characterised signal for PD-L1 induction is interferon-γ (IFNγ), which is predominantly produced by T helper cells, although many of the signals have not yet been defined completely. Excessive induction of PD1 on T cells in the setting of chronic antigen exposure can induce an exhausted or anergic state in T cells.**

2.3.4 Medicines that target PD-L1

Atezolizumab (brand name Tecentriq) is a monoclonal antibody that binds directly to PD-L1 [11]. PD-L1, also known as B7-H1, is the major PD-1 ligand that is expressed on cells from solid tumours [6].

PD-L1 checkpoint inhibitors such as atezolizumab block PD-1 from binding to PD-L1 but not PD-L2, so PD-1/PD-L2-mediated inhibitory signals remain [4, 11]. Tumour regression or non-progression may result from the restored anti-tumour responses produced by these anti-cancer agents [4].

Like PD-1 checkpoint inhibitors, T-cell activation from the use of PD-L1 checkpoint inhibitors can result in immunologic adverse effects [4].

Tecentriq is currently the only atezolizumab–containing medicine available in New Zealand. Tecentriq has been approved for use since April 2017, but is not funded by PHARMAC (at August 2017).

2.3.5 Summary

Below is a summary of the role of immune checkpoints in anti-tumour immune responses. This begins with T-cell activation and the subsequent up-regulation of CTLA-4 and then PD-1. Figure 3 and associated text has been taken from Luke and Ott 2015 [4].

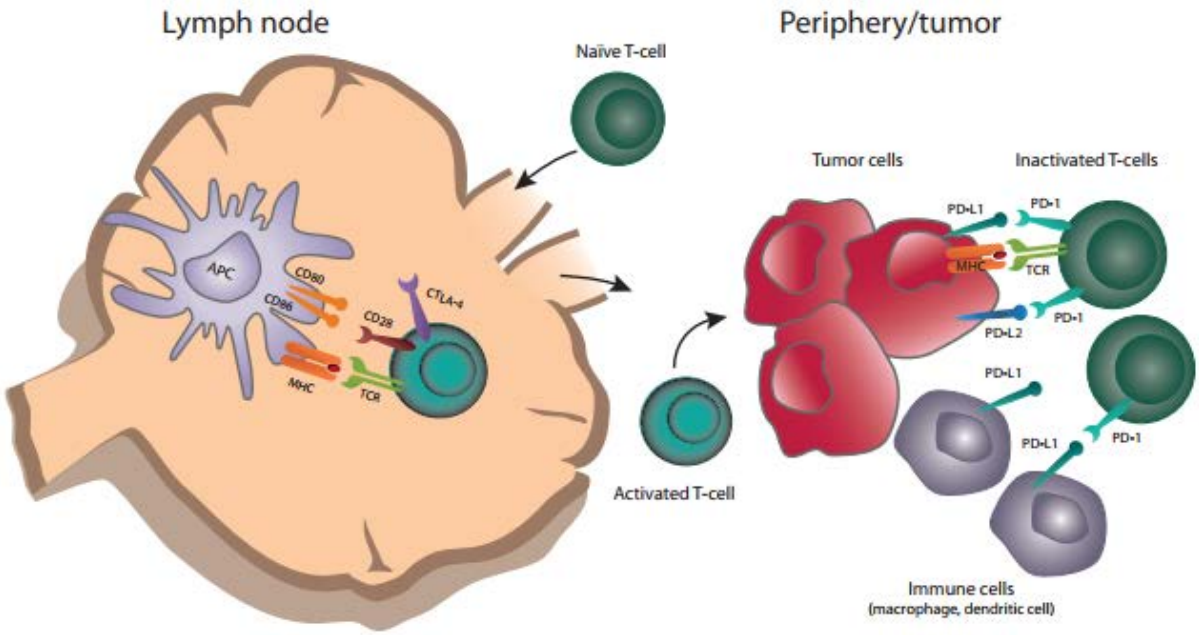


Figure 3 Role of CTLA-4 and PD-1 in anti-tumour immune responses. Naïve T cells are primed by antigens presented by antigen-presenting cells (APCs) in the context of MHC (signal 1), as well as co-stimulatory binding of CD28 to B7 (CD80/86) (signal 2). T cells up-regulate CTLA-4 shortly after activation. Ligation of CTLA-4 with CD80 or CD86 limits T-cell activation and proliferation. Activated T cells traffic to the periphery and encounter tumour antigens at the tumour site. PD-1 is up regulated on T cells after prolonged activation; binding to PD-1 ligands (PD-L1 or PD-L2) expressed by tumour or other immune cells, including macrophages and dendritic cells, causes T cell activation and dampens an ongoing anti-tumour immune response. Image and text taken from Luke and Ott [4].

2.4 Data sheets

2.4.1 New Zealand

The table below provides a summary of wording present in data sheets for ipilimumab, nivolumab, pembrolizumab and atezolizumab at 20 July 2017. Due to the anti-tumour mechanism of action these medicines have, these immunotherapies also generate immune-related adverse events. The focus in the table is therefore on immune-related warnings and precautions and adverse events in data sheets for immune checkpoint inhibitors.

	Ipilimumab (CTLA-4)	Nivolumab (PD-1)	Pembrolizumab (PD-1)	Atezolizumab (PD-L1)
Immune-related gastrointestinal reactions				
Warnings and Precautions	Extensive information on GI reactions in general.	Limited information - Colitis not GI reactions in general	Limited information - Colitis not GI reactions in general	Limited information - Colitis not GI reactions in general
Adverse events	Extensive information on GI reactions in general.	Limited information - Colitis not GI reactions in general	Limited information - Colitis not GI reactions in general	Limited information - Colitis not GI reactions in general
Immune-related hepatotoxicity				
Warnings and Precautions	✓	Limited information - Hepatitis specifically mentioned	✓	✓
Adverse events	✓	✓	✓	✓
Immune-related skin adverse reactions				
Warnings and Precautions	✓	✓	✓	X
Adverse events	✓	✓	Skin ADRs are listed but not specifically as immune-mediated adverse reactions	Skin ADRs are listed but not specifically as immune-mediated adverse reactions
Immune-related neurological adverse reactions				
Warnings and Precautions	✓	✓	Section not present but Guillain-Barre syndrome listed under 'Other immune-mediated adverse reactions'	Section not present but information is included under 'Immune-related neuropathy'
Adverse events	✓	✓	X	Section not present but information is included under 'Immune-related neuropathy'
Immune-related endocrinopathy				
Warnings and Precautions	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓
Immune-related nephritis and renal dysfunction				
Warnings and Precautions	Section not present but glomerulonephritis listed under 'Other immune-related adverse reactions'	✓	Limited information – Nephritis listed, not other renal disorders	X

Adverse events	✓	✓	Limited information – Nephritis listed, not other renal disorders	X
Immune-related pneumonitis				
Warnings and Precautions	Section not present but pneumonitis listed under 'Other immune-related adverse reactions'	✓	✓	✓
Adverse events	✓	✓	✓	✓
Other immune-related adverse reactions				
Warnings and Precautions	Uveitis, eosinophilia, lipase elevation, glomerulonephritis, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, pneumonitis	Myotoxicity (myositis, myocarditis, rhabdomyolysis)	Uveitis, myositis, Guillain-Barre syndrome, pancreatitis, myocarditis	X
Adverse events	Glomerulonephritis, pneumonitis, eosinophilia, haemolytic anaemia, increased lipase, increased amylase	Pancreatitis, uveitis, hypopituitarism, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, rhabdomyolysis	X	X
Immune-related pancreatitis				
Warnings and Precautions	X	X	Section not present but pancreatitis listed under 'Other immune-related reactions'	✓
Adverse events	✓	Section not present but pancreatitis listed under 'Gastrointestinal immune-related reactions'	X	✓
Immune-related neuropathies				
Warnings and Precautions	Section not present but some neuropathies listed under 'Other immune-related adverse reactions'. Sensory neuropathy listed under	Section not present but autoimmune neuropathy listed under 'Immune-related neurological adverse reactions'	Section not present but Guillain-Barre syndrome listed under 'Other immune-related adverse reactions'	✓

	'Immune-related neurological adverse reactions'			
Adverse events	X	Section not present but autoimmune neuropathy listed under 'Immune-related neurological adverse reactions'	X	✓
Immune-related meningoencephalitis (Definition: CNS infection manifesting signs and symptoms consistent with inflammation of the meninges and brain parenchyma [17]. It is a term that recognises the overall between a patient having features of both meningitis and encephalitis [18]				
Warnings and Precautions	Section not present but neuropathy listed under 'Immune-related neurological adverse reactions'	Section not present but encephalitis listed under 'Immune-related neurological adverse reactions'	X	✓
Adverse events	X	Section not present but encephalitis listed under 'Immune-related neurological adverse reactions'	X	✓

Comments:

The table indicates there is a range of immune-related adverse events listed in the data sheets. There is also some variation in the level of detail between the products.

Information relating to immune-related adverse events is included in both the warnings and precautions and adverse events section of the data sheets for the four immune checkpoint inhibitors. Some information is present in the warnings and precautions section only (eg, pembrolizumab).

The data sheets for ipilimumab, nivolumab and pembrolizumab state that immune-related adverse reactions can occur weeks to months after the last dose. The data sheet for atezolizumab does not mention this.

Monitoring guidance in the data sheets – All four data sheets include information in section 4.4 (Special warnings and precautions for use) regarding the need to carefully monitor patients for immune-mediated adverse events and information on treatment.

2.4.2 Australia

With reference to immune-mediated adverse reactions, the Australian Product Information (PI) for pembrolizumab, nivolumab and ipilimumab are the same as New Zealand data sheets (warnings and precautions and adverse effects sections). There is no published Australian PI for atezolizumab.

2.4.3 United Kingdom

2.4.3.1 Keytruda (pembrolizumab)

There is extensive information in section 4.4 (Special warnings and precautions for use) on immune-related adverse reactions. Sub-sections include:

- Immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis, immune-related endocrinopathies, immune-related skin adverse reactions and other immune-related adverse reactions.

There is also extensive information relating to these immune-related adverse reactions in section 4.8 (Undesirable effects).

2.4.3.2 Yervoy (ipilimumab)

There is extensive information in section 4.4 (Special warnings and precautions for use) on immune-related adverse reactions. Sub-sections include:

- Immune-related gastrointestinal reactions, immune-related hepatotoxicity, immune-related skin adverse reactions, immune-related neurological reactions, immune-related endocrinopathy and other immune-related adverse reactions.

There is also extensive information relating to these immune-related adverse reactions in section 4.8 (Undesirable effects).

2.4.3.3 Opdivo (nivolumab)

There is extensive information in section 4.4 (Special warnings and precautions for use) on immune-related adverse reactions. Sub-sections include:

- Immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies, immune-related skin adverse reactions and other immune-related adverse reactions.

There is also extensive information relating to these immune-related adverse reactions in section 4.8 (Undesirable effects).

2.4.3.4 Tecentriq (atezolizumab)

At 8 August 2017 there is no published SPC for Tecentriq. The marketing authorisation application for Tecentriq is pending a decision by the European Commission [19].

Comments:

The New Zealand and international product information reviewed all contain a range of immune-related adverse reactions. These adverse reactions are not unexpected due to the medicines' mechanism of action.

The sub-sections listed in the UK SPC's are all included in the NZ data sheets for the respective products.

2.5 Recent reviews by international regulators

This section includes a summary of recent reviews carried out by international regulators relating to the use of immune checkpoint inhibitors.

2.5.1 Medicines and Healthcare products Regulatory Agency (MHRA) [20]

In July 2017 the MHRA published a Drug Safety Update article on reports of organ transplant rejection in patients treated with nivolumab or pembrolizumab. The article notes that ipilimumab may also increase the risk of graft rejection through its interference with immunosuppressive therapy.

2.5.1.1 Pharmacovigilance Risk Assessment Committee (PRAC) Review [21-23]

A new signal of the risk of transplant rejection from the use of nivolumab and pembrolizumab was detected from EU spontaneous reporting systems and discussed at the 24-27 October 2016 meeting of the PRAC. The PRAC considered that based on the available evidence, from case reports and on biological plausibility, a causal association with transplant rejection could not be excluded. The PRAC recommended that Marketing Authorisation Holders (MAH) for Opdivo (nivolumab) and Keytruda (pembrolizumab) submit a review of cases of transplant rejection.

The MAHs provided a response which was discussed at the PRAC meeting of 6-9 March 2017.

After considering the available evidence, the PRAC concluded that the MAHs should update their product information to add a warning on the risk of solid organ transplant rejection reported in the post-marketing setting in patients treated with PD-1 inhibitors. Solid organ transplant rejection should also be added as an undesirable effect (frequency unknown) for pembrolizumab, nivolumab monotherapy and nivolumab in combination with ipilimumab.

Comment:

Pembrolizumab (Keytruda)

Solid organ transplant rejection is listed as an immune-mediated adverse reaction in the warnings and precautions for use section of the Keytruda data sheet (at 27 July 2017). This risk is not listed in the adverse events section.

Nivolumab (Opdivo)

Organ transplant rejection is not listed in the data sheet for nivolumab (at 18 August 2017). [redacted]

Ipilimumab (Yervoy)

The possibility of an increased risk of graft rejection is listed in the precautions section of the Yervoy data sheet. The data sheet states 'Ipilimumab is a T-cell potentiator that enables the immune response and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection'. This risk is not listed in the adverse events section.

Atezolizumab (Tecentriq)

This risk is not listed in the data sheet for this medicine. At the time of this report the licencing of this medicine was still pending a decision by the European Commission.

2.5.2 Health Canada [24]

In March 2017 Health Canada published a Dear Healthcare Professional Letter on their website regarding the risk of severe skin reactions (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) associated with the use of pembrolizumab (Keytruda).

Comment:

Information on the risk of SJS and TEN is present in both the dose and administration section and the warnings and precautions section of the New Zealand Keytruda data sheet.

2.5.3 [redacted]

[redacted]

Comment:

Medsafe has not received any reports of transplant rejection for nivolumab or pembrolizumab. [redacted]. The data sheet for Keytruda (pembrolizumab) states that solid organ transplant rejection has been reported in the post-marketing setting in patients treated with Keytruda. The data sheet also notes that treatment with Keytruda may increase the risk of rejection in solid organ transplant recipients.

No information on transplant rejection is included in the New Zealand data sheet for Opdivo (nivolumab) (see comments above under section 2.5.1.1).

3.0 SCIENTIFIC INFORMATION

3.1 Summary of Periodic Benefit Risk Evaluation Reports (PBRER)

This section includes a brief overview of PBRERs that have been submitted by the companies to Medsafe. The information focusses on what immune-mediated reactions have been identified by the company as important and potential risks for each of the immune checkpoint inhibitors.

3.1.1 Keytruda (pembrolizumab)

[redacted]

[redacted]

Comments:

The New Zealand data sheet lists all immune-mediated adverse reactions that have been listed by the company as important identified risks.

3.1.2 Opdivo (nivolumab)

[redacted]

[redacted]

Comments

The New Zealand data sheet lists all immune-mediated adverse reactions that have been listed by the company as important identified risks.

3.1.3 Yervoy (ipilimumab)

[redacted]

Comments

The New Zealand data sheet lists all immune-mediated adverse reactions that have been listed by the company as important identified risks.

[redacted]

[redacted]

3.1.4 Tecentriq (atezolizumab)

[redacted]

[redacted]

Comments

The New Zealand data sheet lists all immune-mediated adverse reactions that have been listed by the company as important identified risks [redacted]

3.2 Published literature

3.2.1 Gauchi et al, 2017 [25]

[redacted]

3.2.2 Abdel-Wahab et al, 2016 [26]

The objective of this systematic review of case reports was to describe the occurrence of immune-related adverse events (irAEs) in patients with cancer following checkpoint blockade therapy primarily to identify potentially unrecognised or unusual clinical findings and toxicity.

Medline, EMBASE, Web of Science, PubMed ePubs, and Cochrane CENTRAL were searched with no restriction through August 2015. Studies reporting cases of cancer develop irAEs following treatment with anti CTLA-4 (ipilimumab) or anti PD-1 (nivolumab or pembrolizumab) antibodies were included.

191 publications met inclusion criteria, reporting on 251 cases. The median age of cases was 60 years (26-88 years), 95.6% patients had metastatic melanoma and the majority were treated with ipilimumab (93.2%). Only 10 cases reported pembrolizumab and 7 nivolumab.

Ipilimumab immunotherapy-related adverse events

In the 234 patients who had received ipilimumab, gastrointestinal irAEs were reported in 39.7% of the cases, primarily colitis (34.2%) of which 5.1% developed life threatening intestinal perforation. Autoimmune hepatitis was also reported in 17 patients (7.3%). Hypophysitis was the most commonly reported endocrine irAEs occurring in 29.1% of the cases, followed by thyrotoxicosis or hypothyroidism (4.0% each). Cutaneous irAEs were reported in 60 patients (25.6%), mainly rash and pruritus. Other less frequent irAEs including ophthalmologic, neurologic, hematologic, genitourinary, respiratory, musculoskeletal, and cardiac adverse events were also reported. In addition, well defined systemic autoimmune or inflammatory diseases were reported including sarcoidosis (of the lung, skin, nervous system or muscle), polymyalgia rheumatica/giant cell arteritis, celiac disease, lupus nephritis, dermatomyositis, autoimmune inflammatory myopathy, and Vogt-Koyanagi-like syndrome. A broad spectrum of toxicities were reported for almost every body system.

Pembrolizumab immunotherapy-related adverse events

Ten cases reported irAEs with pembrolizumab. In contrast to ipilimumab, gastrointestinal irAEs were not reported. Cutaneous irAEs were most common, primarily dermatitis, in 30.0% of the cases. Other manifestations included endocrine, ophthalmologic, neurologic, respiratory, and musculoskeletal adverse events. Polymyalgia rheumatica/giant cell arteritis was the only defined systemic autoimmune disease reported.

Nivolumab immunotherapy-related adverse events

Seven cases reported irAEs with nivolumab. Similar to pembrolizumab, gastrointestinal irAEs were not reported. Endocrine irAEs were reported in 3 patients (42.9%), primarily autoimmune thyroid disease. Pneumonitis was also reported in 42.9% of the cases and was complicated by acute respiratory distress syndrome in 28.6%. Cutaneous irAEs were less frequent and defined systemic autoimmune diseases were not reported.

Complete resolution of adverse events occurred in most pembrolizumab and nivolumab cases. However, persistent irAEs and death were reported, mainly in patients treated with ipilimumab.

The authors concluded that evidence from case reports shows that cancer patients develop irAEs following checkpoint blockade therapy, and can occasionally develop clearly defined autoimmune systemic diseases. While discontinuation of therapy and/or treatment can result in resolution of irAEs, long-term sequelae and death have been reported.

Comments
In contrast to CARM data received to date where gastrointestinal adverse events was the most commonly reported system organ class, this review did not identify cases where gastrointestinal adverse events were reported with pembrolizumab (see section 3.3 for CARM data).

3.2.3 Capelli et al, 2016 [27]

The objective of this article was to identify patients in the Johns Hopkins Rheumatology clinics from 2012 to 2016 who have been identified as having new rheumatological symptoms when being treated with ipilimumab (CTLA-4 inhibitor) and/or nivolumab (PD-1 inhibitor) for solid tumours. The authors state that immune checkpoint inhibitors can cause immune-related adverse events but that these with clinical features similar to rheumatic disease have not been well described.

13 patients who received immune checkpoint inhibitors and developed rheumatological irAEs were identified. Mean age was 58.7 years. Cancer types included melanoma, non-small cell lung cancer, small cell lung cancer and renal cell carcinoma. Immune checkpoint inhibitors regimens included nivolumab or ipilimumab as monotherapy (n=5) or combination nivolumab and ipilimumab (n=8).

Nine of 13 patients developed an inflammatory arthritis, 4 with synovitis confirmed on imaging (3 ultrasound, 1 MRI) and 4 with inflammatory synovial fluid. Four patients developed sicca syndrome with severe salivary hypofunction while on immune checkpoint inhibitors that could not be explained by other medicines. Other irAEs included: pneumonitis, colitis, interstitial nephritis and thyroiditis. All 13 patients were treated with corticosteroids with varying response. Two patients were treated with methotrexate and anti-tumour necrosis factor therapy for inflammatory arthritis.

Limitations of this study include the retrospective nature of the analysis, and that patients reported here received only nivolumab and/or ipilimumab rather than all currently approved ICIs. The patients included had symptoms of sufficient severity to be referred to a rheumatologist. There may be many patients with milder symptoms of rheumatic irAEs who were not referred. The authors' sample of patients was also enriched for participants in clinical trials, as Johns Hopkins is a tertiary referral centre, and nivolumab has been Food and Drug Administration-approved for a short period of time. Patients receiving ICIs outside of clinical trials may be systematically different from those enrolled in trials, and they may also receive different monitoring by their clinicians.

3.2.4 Gonzalez-Rodriguez et al, 2016 [16]

Therapies blocking immune checkpoints have emerged as promising anticancer therapies however these medicines are associated with different toxicities than classic cytotoxics due to their mechanism of action. Immunologic tolerance can be altered and a higher risk for reactions mediated by self-directed antigens may occur. These are known as immune-related adverse events (irAEs). The endocrine, skin and gastrointestinal systems are the most frequently affected. Endocrine irAEs may be serious or life-changing and unlike other irAEs hormone replacement improves symptoms which allows patients to continue therapy and gain benefit. Identifying and managing endocrine irAEs is essential to provide acre and maximise the potential of these medicines.

The authors of this review carried out a search of PubMed and MEDLINE for clinical trials published before 30 June 2015.

<u>CTLA-4 Inhibitors (ipilimumab)</u>

The frequency and severity of irARs with ipilimumab are dose-dependent. Endocrine adverse reactions have been reported in 0-29% of patients. Hypophysitis has emerged as a distinctive irAE of ipilimumab with hypothyroidism and hyperthyroidism next in frequency (Table 1 below).

Table 1 Ranges of reported endocrine adverse events

Agent	Any endocrine (%)	Any thyroid (%)	Hypothyroidism (%)	Hyperthyroidism (%)	Thyroiditis (%)	Hypophysitis (%)	Primary adrenal insufficiency (%)
CTLA-4							
Ipilimumab	0–29 [7, 8]	0–7.4 [24, 25]	0–9 [8, 26]	0–2.8 [27, 28]	0 [65]	0–17.4 [15, 25]	0–1.6 [26, 36]
Tremelimumab	0–8.3 [9, 10]	0–5.2 [9, 17]	0–5 [94, 95]	0–2.9 [94, 95]	0–3.6 [96, 97]	0–2.6 [16, 17]	0–1 [10, 16]
PD1							
Pembrolizumab	0–19.2 [44, 98]	0–19.2 [44, 98]	0–11.5 [44, 99]	0–7.7 [38, 44]	0–5 [40, 100]	0–1.2 [40, 101]	0–4.3 [42, 61]
Nivolumab	0–40 [46, 59]	0–40 [46, 59]	0–40 [46, 59]	0–6.5	0–2.2	0–0.9	0–3.3 [57, 62]
Pidilizumab [48–50]	0	0	0	0	0	0	0
PDL1							
Avelumab	0–10 [38, 102]	4.2–10 [38, 102]	0–6.5 [38, 102]	0–10 [38, 102]	0	0	0
Atezolizumab [65,66,103–111]	0–6	0–6	0–6	0	0	0–1	0
Durvalumab [58, 112–115]	2.3–11	2.3–8.7	2.3–4.8	0–3.9	0–1.3	0	0–0.4
Combinations							
Ipilimumab + nivolumab [68, 69, 108–110, 116, 117]	16.7–50	10–50	4–27	0–30	0–4	0–11.7	0–8
Ipilimumab + pembrolizumab [70, 71]	27.3–27.8	18.1–24	6–13.6	4.5–6	0–12	0–9.1	0–6
Durvalumab + tremelimumab [111]	5.9	5.9	5.9	0	0	0	0

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death receptor-1; PD-L1, programmed death receptor 1 ligand.

Ipilimumab related irARs occur in a well-defined characteristic timing pattern (Figure 4). The first to appear are usually skin-related (developing during second or third week of treatment up until the 10th week). Digestive system AEs usually occur between weeks 5 and 10 and hepatic AEs from weeks 6 to 14. Endocrine AEs typically occur after the sixth or seventh week (median time to onset 7-20 weeks). Because the function of the gland is often permanently damaged, endocrinopathies are usually not resolved. Hormone production can however be successfully substituted.

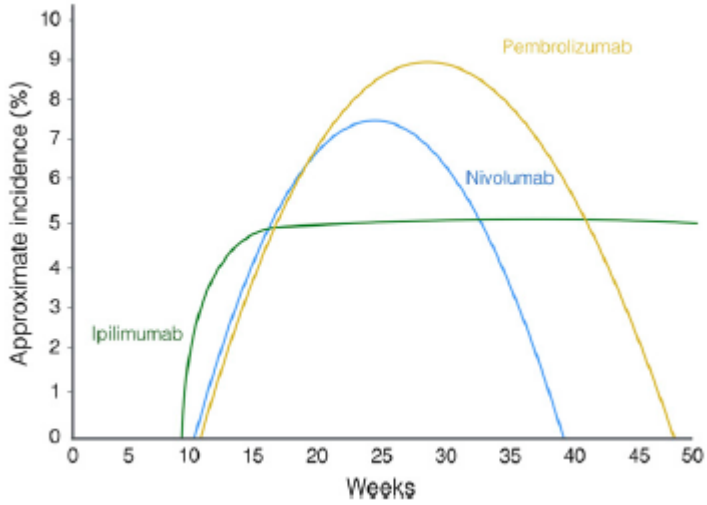


Figure 4 Timing pattern of endocrine adverse events

The incidence of hypophysitis with ipilimumab varies between 0 and 17.4% with a clear dose-dependent relationship. CTLA-4 blockade-relate hypophysitis is more frequently reported in men whereas sporadic hypophysitis is more common in women.

Ipilimumab induces thyroid disorders in 0-7.4% of the patients treated. Hypothyroidism is the most frequent (0-9%) followed by hyperthyroidism (0-2.8%). Thyroiditis has not been reported.

PD-1 and PD-L1 inhibitors (pembrolizumab, nivolumab and atezolizumab)

Because of the different mechanisms of action between PD-1/PD-L1 and CTLA-4 inhibitors, the incidence of endocrinopathies may differ. The CTLA-4 blocking pathway acts on the triggering stage of the autoimmune process and the PD-1/PD-L1 blockade occurs in the modulating phase.

Endocrinopathies due to pembrolizumab and nivolumab have similar median onset times (10 and 11 weeks respectively). The main difference between the two medicines seems to be the time to resolution of the event (48 v 38 weeks).

Hypophysitis was noted to be infrequent (maximum incidence of 1.2% for pembrolizumab and 0.9% for nivolumab).

Thyroid disorders were common in anti PD1 trials (0-19.2% for pembrolizumab and 0-18.5% for nivolumab). For both medicines, hypothyroidism is the most prevalent toxicity followed by hyperthyroidism and thyroiditis.

Fewer endocrine AEs have been reported with PD-L1 inhibitors (atezolizumab – maximum reported incidence of 6%). Endocrinopathies associated with PD-L1 inhibitors are almost all thyroid-related.

CTLA-4 and PD-1/PD-L1 combined blockade

It is suggested that blocking both CTLA-4 and PD-1/PD-L1 pathways has a synergistic effect however as expected an increase in toxicity prevalence and severity is seen. Endocrinopathies occur in 14-50% of patients treated with combinations with thyroid AEs and hypophysitis the most frequent (7-28% and 0-12.8% respectively).

Clinical presentation and practical management

The authors consider that routine screening with thyroid function tests is recommended at baseline, before each dose and every 6-12 weeks for the first 6 months after completion of treatment because of the high incidence of thyroidopathies. The figures below show the suggested management of serious endocrine adverse events and of thyroid dysfunction.

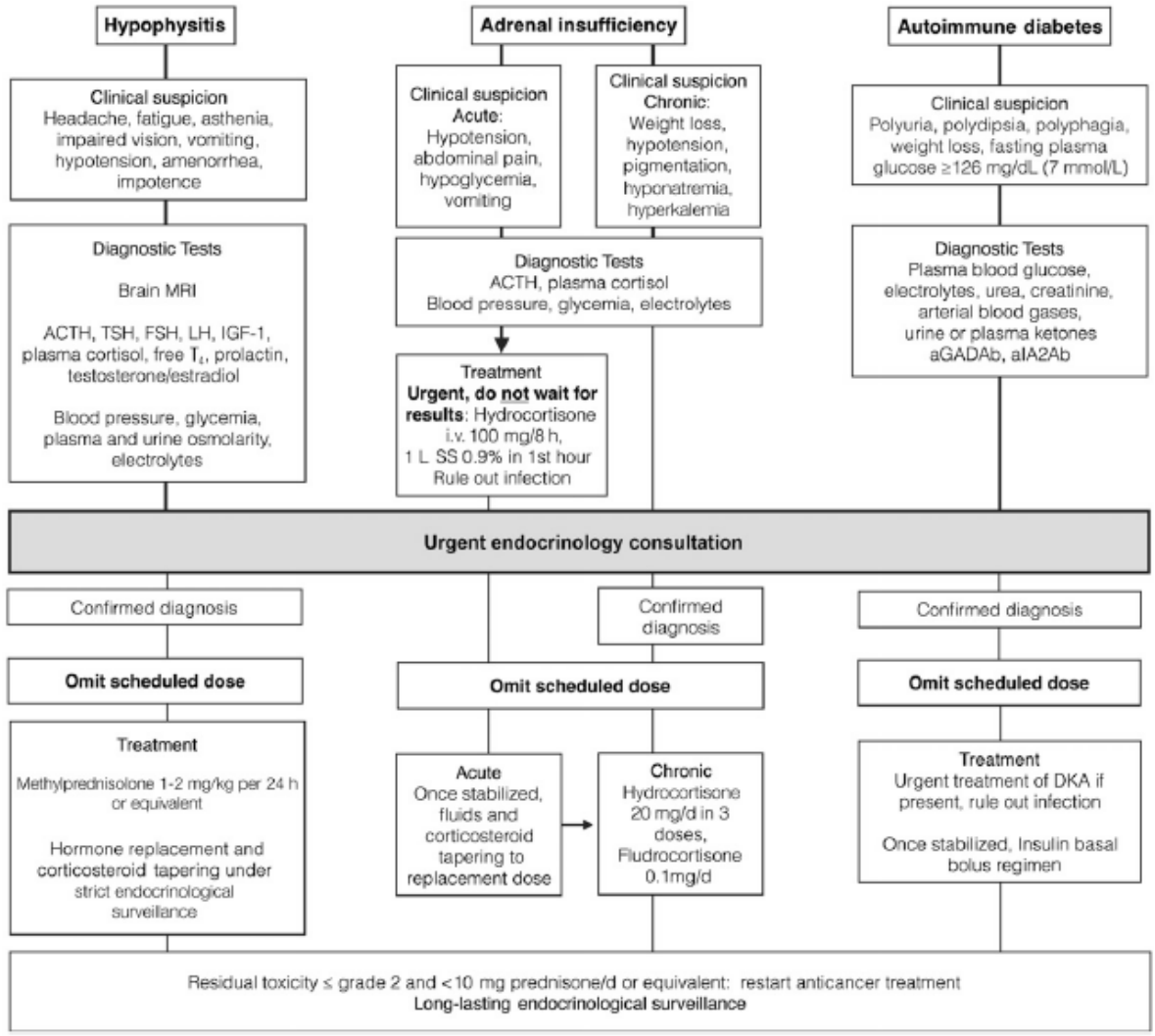


Figure 5 Suggested management of serious endocrine adverse events

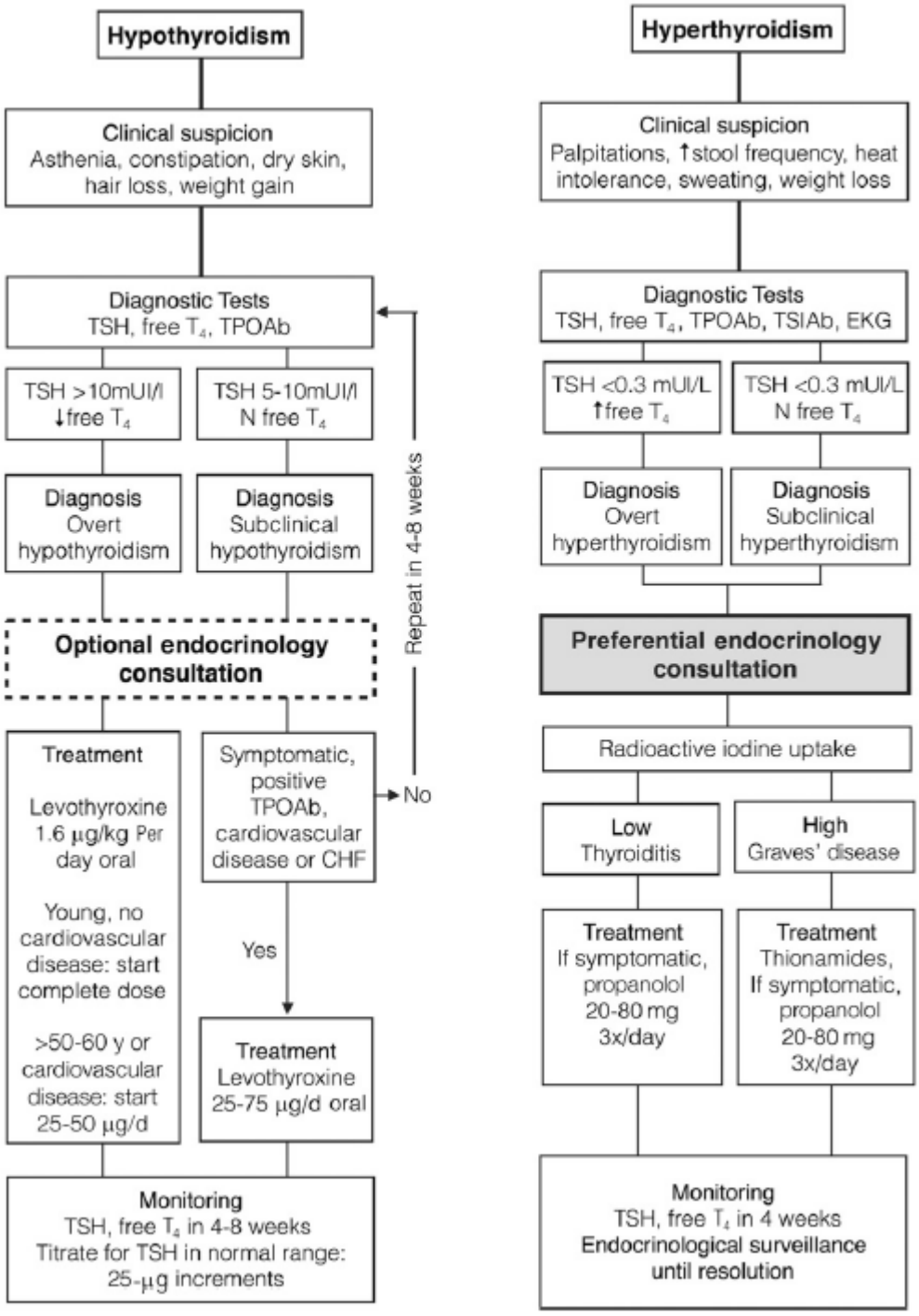


Figure 6 Suggested management of thyroid dysfunction

The authors conclude that irAEs affecting the endocrine system are frequent and generally mild. Thyroid disorders are common and hypophysitis is characteristic of ipilimumab. Combining agents increases the frequency and severity of endocrinopathies and healthcare professionals need to be cautious of life-threatening conditions if not recognised. The authors note the study of endocrine AEs is made difficult by inconsistent terminology in clinical trials and establishing clear definitions is important. Although most endocrinopathies are irreversible, correct management of these can allow the continuation of immunotherapy with a small impact on the patient's quality of life.

Comments
Hypophysitis and thyroid disorders are listed in the Yervoy (ipilimumab) data sheet.

3.2.5 Sznol et al, 2016 [13]

[redacted]

3.2.6 Bertrand et al, 2015 [28]

The objective of this systematic review and meta-analysis was to assess the incidence and nature of irAEs in oncologic patients receiving anti-CTLA-4 antibodies (ipilimumab and tremelimumab).

A systematic search of literature up to February 2014 was performed in MEDLINE, EMBASE, and Cochrane databases to identify relevant articles. Paired reviewers independently selected articles for inclusion and extracted data. Pooled incidence was calculated.

The literature search identified 491 articles in databases and manual searches retrieved five additional articles. Among these 496 articles, 373 were excluded after reading of the abstracts due to duplicate articles, oncologic treatment in combination with other drugs, review articles, or basic research. Finally, 123 articles were fully reviewed and 81 were considered relevant for the present study: 24 clinical trials and 57 case reports.

1265 patients from 22 clinical trials were included for meta-analysis to assess the incidence of irAEs with anti-CTLA-4 treatment (Table 3).

Table 3 Characteristics of studies included for meta-analysis

Trial	Design	Cancer	Enrollment size	Anti-CTLA-4	Dose (mg/kg)	CTC for AE version
Hodi [7]	RCT, phase III	Melanoma	676	Ipilimumab	3	3
Wilgenhof [14]	Prospective observational study	Melanoma	50	Ipilimumab	3	4
Delyon [15]	Prospective observational study	Melanoma	96	Ipilimumab	3	4
Margolin [16]	Open label, phase II	Melanoma	72	Ipilimumab	10	3
Hamid [17]	Randomized, double blind, phase II	Melanoma	82	Ipilimumab	3; 10	n/a
Danielli [18]	Single arm, phase II	Melanoma	13	Ipilimumab	10	3
Wolchok [19]	Randomised phase II, dose ranging study	Melanoma	217	Ipilimumab	0.3; 3; 10	3
O'Day [20]	Multicenter, single arm, phase II	Melanoma	155	Ipilimumab	10	3
Hersh [21]	RCT, phase II	Melanoma	74	Ipilimumab	3	2
Weber [22]	Randomized, double blind, phase II	Melanoma	115	Ipilimumab	10	3
Yang [23]	Randomized, double blind, phase II, dose ranging study	Renal cell	61	Ipilimumab	1; 3	n/a
Downey [24]	Multicenter, single arm, phase II	Melanoma	139	Ipilimumab	9	n/a
Ku [25]	Compassionate use trial	Melanoma	53	Ipilimumab	10	3
Di Giacomo [26]	Single arm, phase II	Melanoma	27	Ipilimumab	10	3
Royal [27]	Single arm, phase II	Pancreatic	27	Ipilimumab	3	3
Le DT [28]	Randomized, open label, phase IB	Pancreatic	30	Ipilimumab	10	3
Weber [29]	Phase I/II	Melanoma	88	Ipilimumab	n/a	n/a
Slovin [30]	Non randomized, open label, multicenter, phase I/II	Prostate	71	Ipilimumab	3; 5; 10	3
Calabro [31]	Open label, single arm, phase II	Mesothelioma	29	Tremelimumab	15	3
Chung [32]	Multicenter, single arm, phase II	Colorectal	47	Tremelimumab	15	3
Ralph [33]	Single arm, phase II	Gastric and esophageal	18	Tremelimumab	15	2
Ribas [34]	Phase I	Melanoma, renal cell, colon	39	Tremelimumab	10; 15	2

CTC for AE version, Common Terminology Criteria for Adverse Events version; RCT, Research clinical trial; n/a, Non-available

<u>Incidence of immune-related adverse events – data from clinical trials</u>

The overall incidence of all-grade irAEs was 72% (95% CI, 65–79%). The overall incidence of high-grade irAEs was 24% (95% CI, 18–30%). The risk of developing irAEs was dependent of dosage, with incidence of all-grade irAEs being evaluated to 61% (95% CI, 56–66%) for ipilimumab 3 mg/kg and 79% (95% CI, 69–89%) for ipilimumab 10 mg/kg.

Death due to irAEs occurred in 0.86% of patients which often related to colic bowel perforation for patients with colitis.

Nature of immune-related adverse events – data from case reports and retrospective studies

The median time of onset of irAEs was about 10 weeks (IQR, 6–12) after the onset of treatment, corresponding with the first three cycles but varied according to the organ system involved. Such immune activation could also be indicative for tumour-specific T-cell activation and irAE occurrence was associated with clinical response to CTLA-4 blocking in 60% of patients.

Cutaneous irAEs were the most common immune side effect of anti-CTLA-4 treatment and occurred within the first month of treatment. Endocrine irAEs were reported to anti-CTA-4 antibodies and they occurred within an average of 11 weeks but were not dose dependent, unlike other irAEs. Autoimmune hypophysitis was the most frequent endocrine side effect (reported in up to 13% of clinical trials). Most patients presented headache (51.8%: 14/27 patients), asthenia (59.3%: 16/27), erectile dysfunction and decreased libido. Visual disturbances were rare (one patient). Hypo- and hyperthyroidism secondary to thyroiditis were rare, up to 5.6% in clinical trials. Gastrointestinal irAEs were important and potentially severe immune complications reported with CTLA-4 blocking drugs. Colitis was reported in 21 patients. Clinical manifestations were diarrhoea (95.2%; 20/21), abdominal pain (38.1%; 8/21), rectal blood (23.8%; 5/21) and nausea, with or without fever. Colitis could be life threatening with fatal colic bowel perforation, reported in two patients. Hepatitis was described in up to 19% of clinical trials. One case illustrated ipilimumab-related pancreatitis considered to be immune-related due to detection of anti-pancreas antibodies.

Various neurologic irAEs, such as Guillain-Barré syndrome, transverse myelitis, aseptic meningitis, inflammatory myopathy, orbital myositis or myasthenia, were described. Sarcoidosis, dyspnoea, skin lesions, uveitis [83], organizing pneumonia, lupus nephritis, autoimmune cytopenia, haemophilia A, as well as a case of polymyalgia/giant cell arteritis were also reported.

The authors concluded that the skin and gastrointestinal tract were mostly affected (44% (95% CI, 38–49.5) and 35% (95% CI, 29–41) of cases, respectively, while endocrine and hepatic organs were less affected, in 6% (95% CI, 4–8) and 5% (95% CI, 2–7), respectively. Other events, such as neurologic, hematologic, ophthalmologic, or rheumatologic diseases, were rare. The authors considered that a better knowledge of these irAEs and its management in a multidisciplinary approach will help reduce morbidity and therapy interruptions.

Comments

This review focusses on CTLA-4 inhibitors (ipilimumab (Yervoy)) and noted that death due to irAEs occurred in 0.86% of patients which often related to colic bowel perforation for patients with colitis.

The Yervoy (ipilimumab) data sheet states that fatalities due to gastrointestinal perforation have been reported in clinical trials.

For the other immune checkpoint inhibitors, the data sheets mention that events may be fatal but mostly in relation to severe skin reactions, pneumonitis or hepatitis rather than colitis, gastrointestinal perforation or immune-mediated adverse effects in general.

3.2.7 Camacho, 2015 [14]

This review looked at the biology, safety, efficacy and future considerations of CTLA-4 blockade with ipilimumab.

Considering the immune stimulatory mechanism of ipilimumab, it is not surprising that the safety profile for ipilimumab includes inflammatory, immune-mediated side effects which may resemble or differ from the side effects observed after therapy with other cytotoxic agents.

A recent analysis of 14 pooled ipilimumab clinical trials has evaluated the overall safety profile of the agent. All patients in the studies included in the retrospective analyses had unresectable stage III or stage IV melanoma and no prior history or clinical evidence of autoimmune disease or treatment with immunosuppressive drugs. This analysis only included those reported between the first dose

and 70 days after the last dose of study therapy. Almost all patients experienced an adverse event (incidence 84.8% for any grade drug-related AE). The most common AEs included those affecting the gastrointestinal (GI) tract (i.e., diarrhoea, nausea, abdominal pain) and skin (i.e., rash, pruritus). The majority of AEs appeared to be related to the agent's mechanism of action. Close supervision and prompt recognition of collateral irAEs may lead to early treatment with corticosteroids and control of the symptoms in a majority of patients however the analysis stated death may still occur in less than 1% of patients.

Treatment guidelines have been developed through the clinical trial development through the clinical trial development for ipilimumab and tremelimumab. These advise initiation of corticosteroids in any patient treated with ipilimumab in which an irAE is suspected (Table 4).

Table 4 Guidelines for recommended management of irAEs

Site	Signs and symptoms	Management
GI	Assess patients for changes in bowel habits and for the following signs and symptoms: diarrhea, abdominal pain, blood or mucus in stool with or without fever, peritoneal signs consistent with bowel perforation, and ileus	Low-grade events: symptomatic management (dietary modifications and loperamide) High-grade events: corticosteroid therapy may be required >7 stools/day over baseline, signs consistent with perforation, or patients with a fever: administer 1–2 mg/kg prednisone or equivalent and then move forward with ensuring differential diagnosis Withhold ipilimumab for moderate reactions until improvement to mild severity or complete resolution; for severe reactions, discontinue ipilimumab
Skin	Evaluate patients for signs and symptoms of pruritus, vitiligo, or maculopapular rash	Mild to moderate: symptomatic management. Topical moisturizers and oatmeal baths may help relieve mild cases Moderate to severe: topical and/or systemic corticosteroids may be required Withhold ipilimumab dosing in patients with moderate to severe signs and symptoms Permanently discontinue ipilimumab in patients with Stevens–Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations
Liver	Run liver function tests (LFTs) before each infusion or more frequently if possible Monitor patients for any signs of hepatitis	Moderate AST or ALT >2.5 times but ≤5 times ULN, or moderate total bilirubin elevation >1.5 times but ≤3 times ULN: withhold ipilimumab dose Severe AST or ALT elevations of >5 times ULN; total bilirubin elevations of >3 times ULN; or failure to complete full treatment course within 16 weeks from administration of first dose: permanently discontinue ipilimumab Grade ≥3 hepatitis: consider corticosteroid therapy
Endocrine	Nonspecific symptoms include: fatigue, headache, changes in mental status, abdominal pain, unusual bowel habits, and hypotension Undertake appropriate blood work	Moderate reactions or symptomatic endocrinopathy: withhold ipilimumab until complete resolution or stable on hormone replacement therapy Patients unable to have their corticosteroid dose reduced to 7.5 mg prednisone or equivalent per day: permanently discontinue ipilimumab Consider long-term hormone replacement therapy as necessary
Neurologic	Encourage patient report of changes in muscle weakness or sensory alternations	New onset or worsening symptoms: may require permanent discontinuation of ipilimumab
Ocular	Assess patients for uveitis, iritis, or episcleritis	Administer corticosteroid drops

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFTs, liver function tests; ULN, upper limit of normal.

Comments

Tremilimumab has not been approved for use in New Zealand.

3.2.8 Hughes et al, 2015 [29]

Autoimmune endocrinopathies, including hypophysitis, hypopituitarism, and thyroiditis, have been reported in trials involving inhibitory CTLA-4 and PD-1 monoclonal antibodies. But autoimmune diabetes has not been definitively linked to these agents.

The authors described the development of new-onset insulin-dependent diabetes in five patients after receiving inhibitory PD-1 antibodies, either as single agent or in combination with other cancer drugs. It was noted that while the patients presented with diverse cancer types, and some had been treated with other immunological agents, their clinical histories were common for PD-1 inhibitor antibody exposure prior to developing autoimmune diabetes.

Time from drug administration to diabetes onset spanned 1 week to 5 months, when patients presented with severe hyperglycaemia or diabetic ketoacidosis (DKA) with elevated HbA1c. Diabetes was a new diagnosis for all but one patient who had pre-existing type 2 diabetes controlled with metformin. Most patients exhibited inappropriately low or undetectable C-peptide (Table 5). All were initiated on insulin therapy upon presentation and remained insulin-dependent for glucose control.

The cases demonstrate temporal correlation between anti-PD-1 treatment and diabetes onset as well as mechanistic support for cancer immunotherapies targeting T-cell regulatory pathways to precipitate autoimmune diabetes. The authors considered other factors that may influence predisposition for hyperglycaemia and autoimmunity included combined use with other immune modulators (patient 1), pancreatic metastases (patient 3) and pre-existing type 2 diabetes (patient 4). Nonetheless, the authors considered the fact that they all developed acute severe hyperglycaemia with ketoacidosis or low/undetectable C-peptide levels is strong evidence for a new and insulin-deficient type of diabetes. Diabetes had previously been reported as an adverse event to PD-L1 inhibitors and one case was reported in 206 subjects treated with nivolumab, but there lacked evidence for an autoimmune mechanism. The authors consider their report demonstrates humoural and cellular autoimmunity in multiple patients with anti-PD-1–induced diabetes and note that although it is difficult to estimate the true incidence of this phenomenon, the five patients in this series represent less than 3% of total subjects who have participated in PD-1/PD-L1 trials at the authors' institution. The author's considered that these cases illustrate the importance of recognising this potential precipitant of autoimmune diabetes in older individuals receiving immunotherapy.

Table 5 Clinical history and key laboratory findings

Patient	Age/sex	Primary diagnosis	Pertinent history	Anti-PD-1 drug	Other chemotoxins	Diabetes presentation	Random C-peptide* and glucose	Time after anti-PD-1	Antibody positivity/titers ^	HLA	Diabetes antigen-specific T cells†
1	55/F	Melanoma	Autoimmune thyroid disease	Nivolumab	Ipilimumab, prednisone	DKA, glucose 532 mg/dL, HbA_{1c} 6.9% (52 mmol/mol)	<0.1 ng/mL and 52 mg/dL	5 months	None	$A2.1^+$, $DR4^+$	0.35%
2	83/F	Non–small-cell lung cancer	Remote smoker	Nivolumab	None	DKA, glucose 350 mg/dL, HbA_{1c} 7.7% (61 mmol/mol)	<0.1 ng/mL and 336 mg/dL	<1 month	GAD65/1.2	$A2.1^+$, $DR4^+$	0.28%
3	63/M	Renal cell carcinoma	Hypertension	Nivolumab	Proleukin, bevacizumab, interferon	Random glucose 247, 340 mg/dL; HbA_{1c} 8.2% (66 mmol/mol)	1.3 ng/mL and 79 mg/dL	4 months	GAD65/1.1, ICA512/1.2, Insulin (IAA)/47	$A2.1^+$, $DR4^+$	2.01%
4	58/M	Small-cell lung cancer	Type 2 diabetes	Nivolumab	Carboplatin/ etoposide, paclitaxel	DKA, glucose 749 mg/dL, HbA_{1c} 9.7% (83 mmol/mol) (from 8.5% [69 mmol/mol] prior)	<0.1 ng/mL and 284 mg/dL 0.6 ng/mL and 523 mg/dL	1 week	GAD65/13819	$A2.1^+$	0.89%
5	64/F	Melanoma	Autoimmune thyroid disease, psoriasis	Pembrolizumab	None	Ketonuria, glucose 703 mg/dL, HbA_{1c} 7.4% (57 mmol/mol)	0.5 ng/mL and 268 mg/dL	<1 month	None	$DR4^+$	N/A

*C-peptide reference range: 1.1–4.4 ng/mL. †Patients 1, 2, 3, and 4 were positive for HLA-A2.1 from screening by flow cytometry using monoclonal antibody BB7.1 (Abcam, Cambridge, MA). HLA-A2.1 tetramers were obtained from the National Institutes of Health Tetramer Core Facility (Atlanta, GA) and loaded with peptides from five diabetes antigens: insulin A chain (GIVEQCCTSI), insulin B chain (HLVEALYLV), preproinsulin (ALWMRLLPL), GAD65 (VMNILLQYVV), and IGRP (LNIDLLWSV) (5). Peripheral blood mononuclear cells (PBMCs) were incubated with the five class I diabetes antigen-containing tetramers. The data shown represent positive staining after subtracting staining with a negative tetramer. PBMCs from $HLA\text{-}A2.1^+$ donors without diabetes served as negative control and showed staining (mean ± 2 SD) of 0.5%. PBMCs were also stained with monoclonal antibodies to CD45RO, CCR7, and CD45RA to identify cellular phenotypes. Flow data were analyzed using FlowJo software version 9.6.1 (Tree Star, Ashland, OR). ^ Diabetic autoantibodies to GAD65, ICA512, and insulin were performed at LabCorp, Burlington, NC. Normal GAD65 titers <0.5 U/mL, ICA512 <1.0 U/mL, and IAA <5.0 U/mL.

3.2.9 Larkin et al, 2015 [30]

This randomised, double-blind, phase 3 study (CheckMate 067) compared nivolumab alone or nivolumab plus ipilimumab with ipilimumab alone in patients with metastatic melanoma. In a 1:1:1 ratio, 945 previously untreated patients with unresectable stage III or IV melanoma were assigned to one of the treatment groups. Progression-free survival and overall survival were co-primary end points.

The three treatment regimens were 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo); 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses, followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond; or 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo). Both nivolumab and ipilimumab were administered by means of intravenous infusion.

Baseline characteristics of the patients at baseline are shown in the table below.

Table 6 Characteristics of the Patients at Baseline

Characteristic	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)	Total (N=945)
Age — yr				
Mean	59	59	61	60
Range	25–90	18–88	18–89	18–90
Age category — no. (%)				
<65 yr	198 (62.7)	185 (58.9)	182 (57.8)	565 (59.8)
≥65 to <75 yr	79 (25.0)	94 (29.9)	89 (28.3)	262 (27.7)
≥75 yr	39 (12.3)	35 (11.1)	44 (14.0)	118 (12.5)
Sex — no. (%)				
Male	202 (63.9)	206 (65.6)	202 (64.1)	610 (64.6)
Female	114 (36.1)	108 (34.4)	113 (35.9)	335 (35.4)
ECOG performance-status score — no. (%)†				
0	238 (75.3)	230 (73.2)	224 (71.1)	692 (73.2)
1	77 (24.4)	83 (26.4)	91 (28.9)	251 (26.6)
2	1 (0.3)	0	0	1 (0.1)
Not reported	0	1 (0.3)	0	1 (0.1)
Metastasis stage — no. (%)				
M1c	184 (58.2)	181 (57.6)	183 (58.1)	548 (58.0)
M0, M1a, or M1b	132 (41.8)	133 (42.4)	132 (41.9)	397 (42.0)
Lactate dehydrogenase — no. (%)				
≤ULN	196 (62.0)	199 (63.4)	194 (61.6)	589 (62.3)
>ULN	112 (35.4)	114 (36.3)	115 (36.5)	341 (36.1)
≤2× ULN	271 (85.8)	276 (87.9)	279 (88.6)	826 (87.4)
>2× ULN	37 (11.7)	37 (11.8)	30 (9.5)	104 (11.0)
Unknown	8 (2.5)	1 (0.3)	6 (1.9)	15 (1.6)
Brain metastases — no. (%)				
Yes	8 (2.5)	11 (3.5)	15 (4.8)	34 (3.6)
No	308 (97.5)	303 (96.5)	300 (95.2)	911 (96.4)
PD-L1 status — no. (%)				
Positive	80 (25.3)	68 (21.7)	75 (23.8)	223 (23.6)
Negative	208 (65.8)	210 (66.9)	202 (64.1)	620 (65.6)
Could not be determined or evaluated	28 (8.9)	36 (11.5)	38 (12.1)	102 (10.8)
BRAF status — no. (%)				
Mutation	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)
No mutation	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)

* There were no significant between-group differences at baseline. PD-L1 denotes programmed death 1 ligand, and ULN upper limit of the normal range.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. A score of 0 indicates no symptoms, 1 mild symptoms, and 2 moderate symptoms, with the patient being ambulatory and capable of all self-care but unable to carry out any work activities. Two patients were inadvertently enrolled in the study: one patient with an ECOG performance-status score of 2 was randomly assigned to the nivolumab group, and one whose ECOG performance-status score was not reported was randomly assigned to the nivolumab-plus-ipilimumab group.

The median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001), and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). In patients with tumours positive for the PD-1 ligand (PD-L1), the median progression-free survival was 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumours, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8 to 7.1].

Treatment-related adverse events of any grade occurred in 82.1% of the patients in the nivolumab group, 95.5% of those in the nivolumab plus-ipilimumab group, and 86.2% of those in the ipilimumab group. The most common adverse events in the nivolumab-plus-ipilimumab group were diarrhoea (in 44.1% of patients), fatigue (in 35.1%), and pruritus (in 33.2%). The incidence of treatment-related adverse events of grade 3 or 4 was also higher in the nivolumab plus-ipilimumab group (55.0%) than in the nivolumab group (16.3%) or the ipilimumab group (27.3%). Treatment-related adverse events of any grade that led to discontinuation of the study drug occurred in 7.7% of the patients in the nivolumab group, 36.4% of those in the nivolumab-plus ipilimumab group, and 14.8% of those in the ipilimumab group (Table 3).

The most frequent adverse events with a potential immunologic cause were diarrhoea (in 2.2% of patients in the nivolumab group, 9.3% of those in the nivolumab-plus-ipilimumab group, and 6.1% of those in the ipilimumab group), colitis (in 0.6%, 7.7%, and 8.7%, respectively) and increased alanine aminotransferase level (in 1.3%, 8.3%, and 1.6%, respectively). Resolution rates of these potential immunologic adverse events were between 85-100% (grade 3 or 4) and as in other studies, most endocrine events did not resolve.

Table 7 Adverse events

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

In this study, patients with previously untreated advanced melanoma, treatment with nivolumab alone or with the combination of nivolumab and ipilimumab resulted in significantly longer progression-free survival and higher objective response rates than did treatment with ipilimumab alone.

The incidence of adverse events in this study was, in general, lowest in the nivolumab group and highest in the combination group. No new safety signals were identified, and there were no drug-related deaths in the combination group. Adverse events were manageable with established treatment guidelines, and most select adverse events resolved with the use of immune-modulatory agents.

3.2.10 Robert et al, 2015 [31]

834 patients with advanced melanoma were assigned in a 1:1:1 ratio to receive pembrolizumab (at a dose of 10 mg per kilogram of body weight) every 2 weeks or every 3 weeks or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks, in this randomised, controlled, phase 3 study (KEYNOTE-006). Primary end points were progression-free and overall survival.

Patients who were 18 years of age or older were eligible for enrolment if they had histologically confirmed, unresectable stage III or IV melanoma and had received no more than one previous systemic therapy for advanced disease. Known BRAF V600 mutational status was required. Other key eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability) and provision of a tumour sample adequate for assessing PD-L1 expression. Excluded from the study were patients who had

received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors and those who had ocular melanoma, active brain metastases or a history of serious autoimmune disease.

Table 8 Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population)

Characteristic	Pembrolizumab Every 2 Wk (N=279)	Pembrolizumab Every 3 Wk (N=277)	Ipilimumab (N=278)
Median age (range) — yr	61 (18–89)	63 (22–89)	62 (18–88)
Male sex — no. (%)	161 (57.7)	174 (62.8)	162 (58.3)
ECOG performance status — no. (%)			
0	196 (70.3)	189 (68.2)	188 (67.6)
1	83 (29.7)	88 (31.8)	90 (32.4)
Elevated baseline LDH level — no. (%)	81 (29.0)	98 (35.4)	91 (32.7)
Metastasis stage — no. (%)†			
M0	9 (3.2)	9 (3.2)	14 (5.0)
M1‡	6 (2.2)	4 (1.4)	5 (1.8)
M1a	21 (7.5)	34 (12.3)	30 (10.8)
M1b	64 (22.9)	41 (14.8)	52 (18.7)
M1c	179 (64.2)	189 (68.2)	177 (63.7)
PD-L1–positive tumor — no. (%)	225 (80.6)	221 (79.8)	225 (80.9)
BRAF V600 mutation — no. (%)	98 (35.1)	97 (35.0)	107 (38.5)
Brain metastasis — no. (%)	23 (8.2)	27 (9.7)	28 (10.1)
Line of previous systemic therapy — no. (%)§			
0	183 (65.6)	185 (66.8)	181 (65.1)
1	96 (34.4)	91 (32.9)	97 (34.9)
Type of previous systemic therapy — no. (%)¶			
Chemotherapy	36 (12.9)	41 (14.8)	29 (10.4)
Immunotherapy	8 (2.9)	7 (2.5)	12 (4.3)
BRAF or MEK inhibitor or both	50 (17.9)	45 (16.2)	56 (20.1)

* There were no significant differences among the groups. ECOG denotes Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, and PD-L1 programmed cell death 1 ligand 1.
† Details regarding metastasis stages in melanoma are provided in Table S3 in the Supplementary Appendix.
‡ Further classification of the metastasis stage was not provided.
§ One patient (0.4%) in the group receiving pembrolizumab every 3 weeks had received two previous systemic therapies.
¶ Only therapy administered for advanced or metastatic disease is listed.

The estimated 6-month progression-free-survival rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (hazard ratio for disease progression, 0.58; P<0.001 for both pembrolizumab regimens versus ipilimumab; 95% confidence intervals [CIs], 0.46 to 0.72 and 0.47 to 0.72, respectively). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively (hazard ratio for death for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 to 0.83; P = 0.0005; hazard ratio for pembrolizumab every 3 weeks, 0.69; 95% CI, 0.52 to 0.90; P = 0.0036).

The mean duration of exposure was 164 days among patients receiving pembrolizumab every 2 weeks, 151 days among those receiving pembrolizumab every 3 weeks and 50 days for those receiving ipilimumab. Rates of treatment-related adverse events of grade 3 to 5 severity were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%). The time until the onset of the first grade 3 to 5 adverse event, regardless of attribution, was longer in the pembrolizumab groups. Permanent discontinuation of a study drug because of treatment-related

adverse events was lower in each pembrolizumab group than in the ipilimumab group (4.0%, 6.9%, and 9.4%, respectively.

The most common treatment-related adverse events associated with pembrolizumab were fatigue, diarrhoea, rash and pruritus. For ipilimumab, the most frequent adverse events were pruritus, diarrhoea, fatigue and rash. Adverse events of special interest (immune-related) most frequently seen with pembrolizumab were hypothyroidism and hyperthyroidism. Colitis and hepatitis were reported in more than 1% of patients treated with pembrolizumab. In the ipilimumab group, the most common adverse event of special interest was colitis, which occurred in 8.2% of patients. Grade 3 to 4 events that were reported in more than 1% of ipilimumab-treated patients were colitis (7.0%) and inflammation of the pituitary gland (i.e., hypophysitis) (1.6%). Hypothyroidism and hyperthyroidism were more frequent in the pembrolizumab groups, whereas colitis and hypophysitis were more frequent in the ipilimumab group.

Table 9 Adverse Events in the As-Treated Population

Adverse Event	Pembrolizumab Every 2 Wk (N=278)		Pembrolizumab Every 3 Wk (N=277)		Ipilimumab (N=256)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)					
Related to treatment*						
Any	221 (79.5)	37 (13.3)	202 (72.9)	28 (10.1)	187 (73.0)	51 (19.9)
Occurring in ≥10% of patients in any study group						
Fatigue	58 (20.9)	0	53 (19.1)	1 (0.4)	39 (15.2)	3 (1.2)
Diarrhea	47 (16.9)	7 (2.5)	40 (14.4)	3 (1.1)	58 (22.7)	8 (3.1)
Rash	41 (14.7)	0	37 (13.4)	0	37 (14.5)	2 (0.8)
Pruritus	40 (14.4)	0	39 (14.1)	0	65 (25.4)	1 (0.4)
Asthenia	32 (11.5)	1 (0.4)	31 (11.2)	0	16 (6.3)	2 (0.8)
Nausea	28 (10.1)	0	31 (11.2)	1 (0.4)	22 (8.6)	1 (0.4)
Arthralgia	26 (9.4)	0	32 (11.6)	1 (0.4)	13 (5.1)	2 (0.8)
Vitiligo	25 (9.0)	0	31 (11.2)	0	4 (1.6)	0
Adverse event of special interest†						
Hypothyroidism	28 (10.1)	1 (0.4)	24 (8.7)	0	5 (2.0)	0
Hyperthyroidism	18 (6.5)	0	9 (3.2)	0	6 (2.3)	1 (0.4)
Colitis	5 (1.8)	4 (1.4)	10 (3.6)	7 (2.5)	21 (8.2)	18 (7.0)
Hepatitis	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)	3 (1.2)	1 (0.4)
Hypophysitis	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	6 (2.3)	4 (1.6)
Pneumonitis	1 (0.4)	0	5 (1.8)	1 (0.4)	1 (0.4)	1 (0.4)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Uveitis	1 (0.4)	0	3 (1.1)	0	0	0
Myositis	0	0	2 (0.7)	0	1 (0.4)	0
Nephritis	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)

* The relationship between an adverse event and a study drug was attributed by the investigator. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks, except for hypothyroidism, hyperthyroidism, and colitis, which are reported as adverse events of special interest.

† The listed adverse events of special interest include related terms and are provided regardless of attribution to a study drug. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks.

This randomised, controlled, phase 3 study found that two regimens of pembrolizumab, as compared with ipilimumab, improved both progression-free and overall survival in patients with advanced melanoma. The authors concluded that the PD-1 inhibitor pembrolizumab had less high-grade toxicity than ipilimumab in patients with advanced melanoma.

Comments

In general, the literature reports that a wide range of immune-mediated events can occur from the use of immune checkpoint inhibitors and gastrointestinal and skin adverse events are commonly noted as being the most frequent. Interestingly, diabetes does not seem to be associated from the use of ipilimumab (Yervoy) as it is with the other immune checkpoint inhibitors. The literature indicates that rates of various immune-related adverse events can differ between the immune checkpoint inhibitors, for example hypothyroidism and hyperthyroidism were the most frequently seen immune-related adverse events seen with pembrolizumab and colitis was the most frequently seen immune-related adverse events seen with ipilimumab (Robert et al, 2015, section 3.2.10)

3.3 CARM data

CARM have received 41 reports reporting either nivolumab, ipilimumab or pembrolizumab as a suspect medicine. 17 reports, reporting 42 reactions, have been received for nivolumab, 7 reports, reporting 14 reactions, have been received for ipilimumab and 17 reports, reporting 41 reactions, have been received for pembrolizumab.

[redacted]

A line listing of the cases can be found in Annex 2. Adverse drug reactions (ADRs) reported (by System Organ Class (SOC)) with all immune checkpoint inhibitors are displayed in Figure 7 below. Figures 8-10 show ADRs for each immune checkpoint inhibitor. When an ADR is in more than one SOC, the primary SOC has been used.

The figures show a range of reactions have been reported in association with immune checkpoint inhibitors in New Zealand. Overall, the most reported reactions fall into the 'General disorders and administration site conditions' and the 'Gastrointestinal disorders' SOCs. Disease progression was the most reported reaction in the 'General disorders and administration site conditions' SOC. Other ADRs were fatigue, malaise, chest tightness/pain, fever, peripheral oedema, abnormal gait and generalised weakness. Diarrhoea was the most reported ADR in the 'Gastrointestinal disorders' SOC (5 cases). Other ADRs were nausea, faecal incontinence, abdominal distension, colitis, constipation, ascites and abdominal pain/distension.

Figure 7 Reported Reactions by System Organ Class for ipilimumab, nivolumab and pembrolizumab

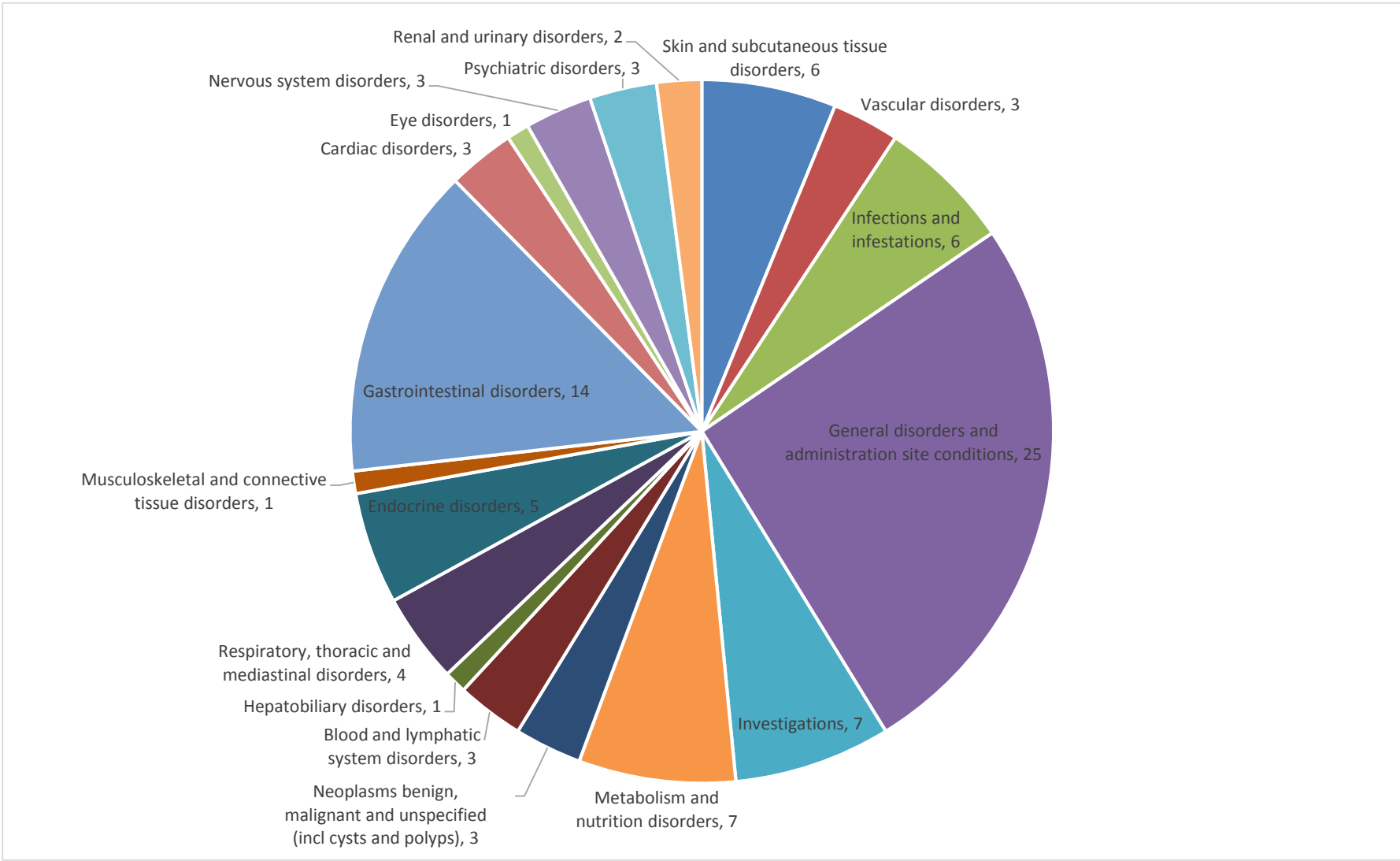


Figure 8 Reported Reactions by System Organ Class for nivolumab

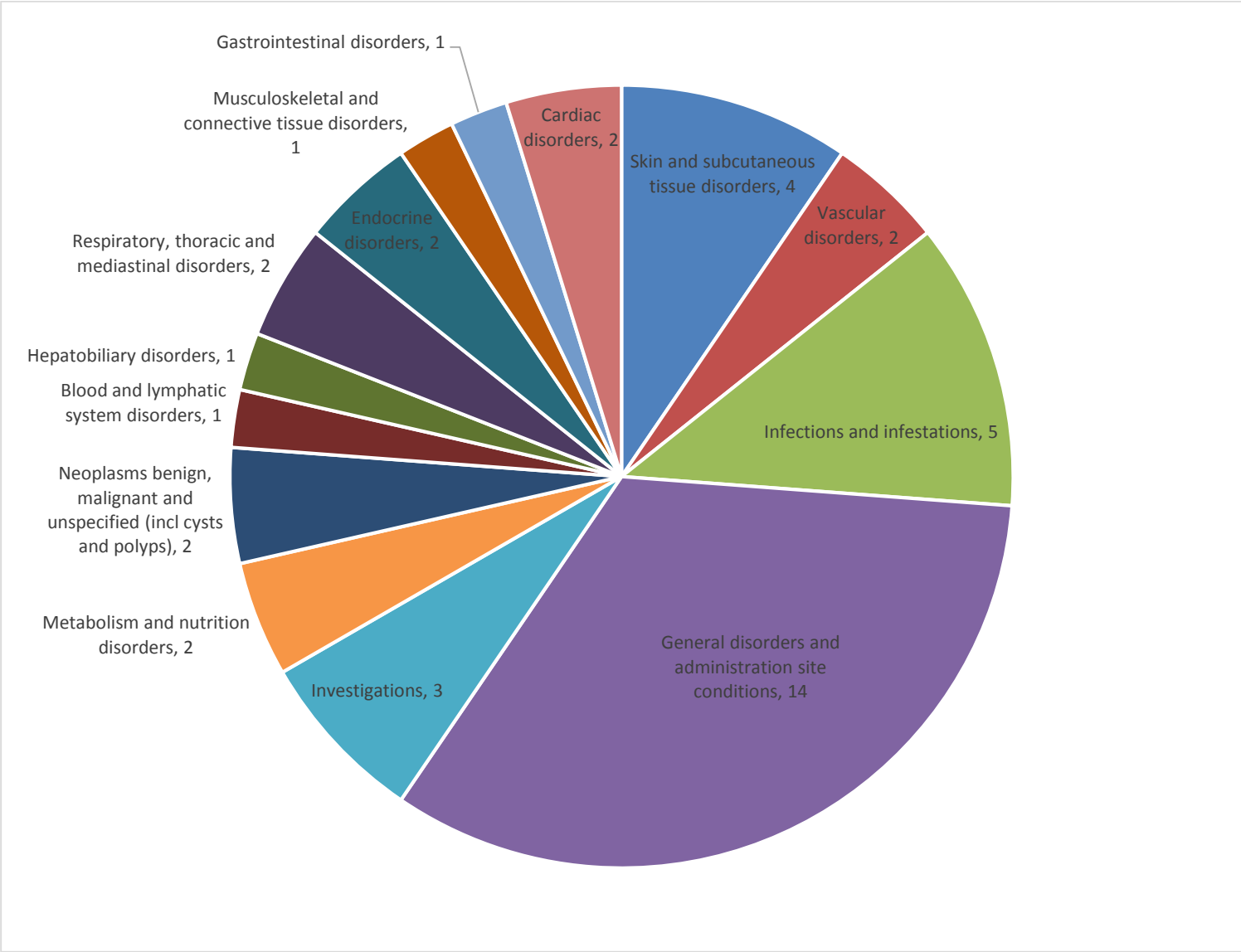


Figure 9 Reported Reactions by System Organ Class for ipilimumab

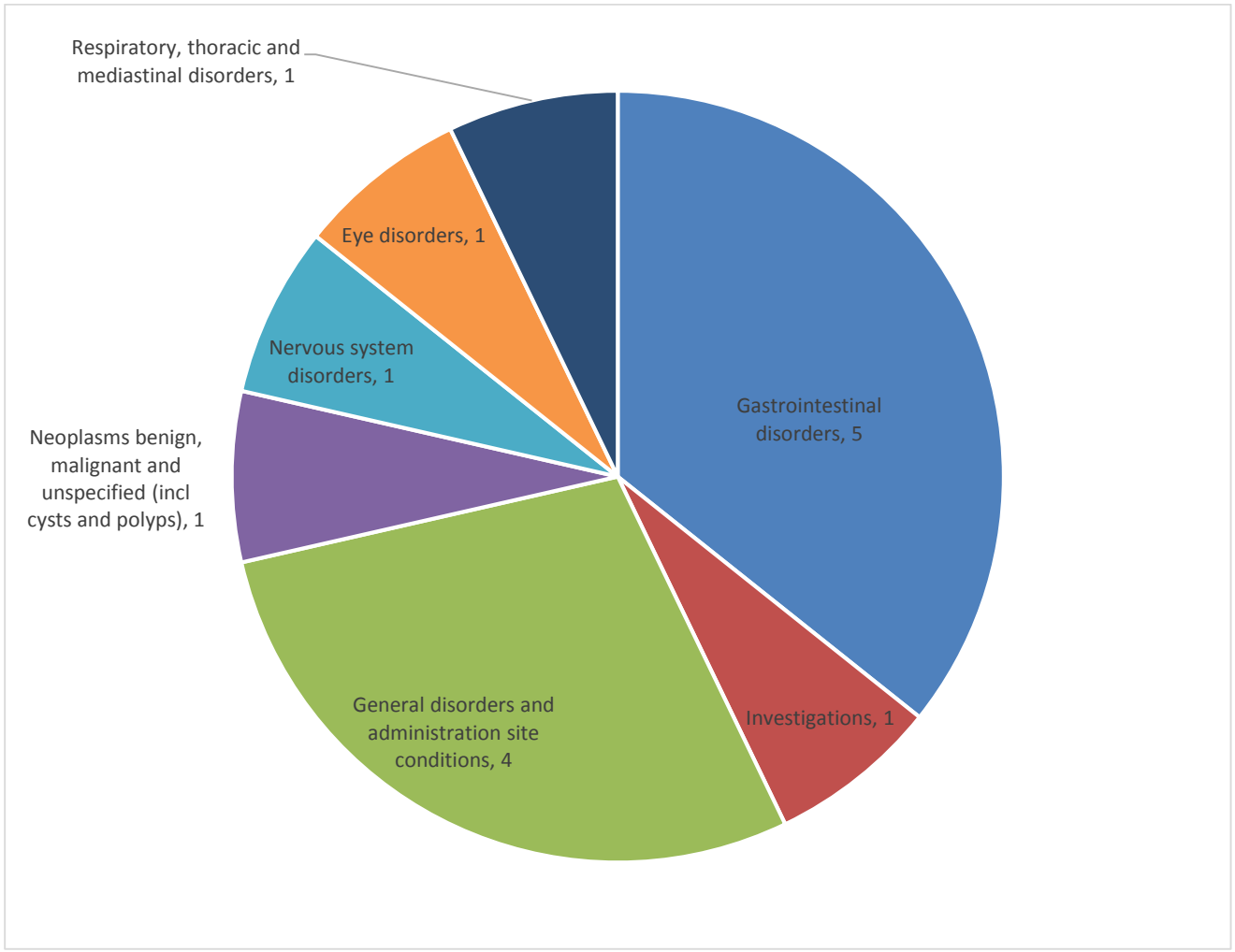
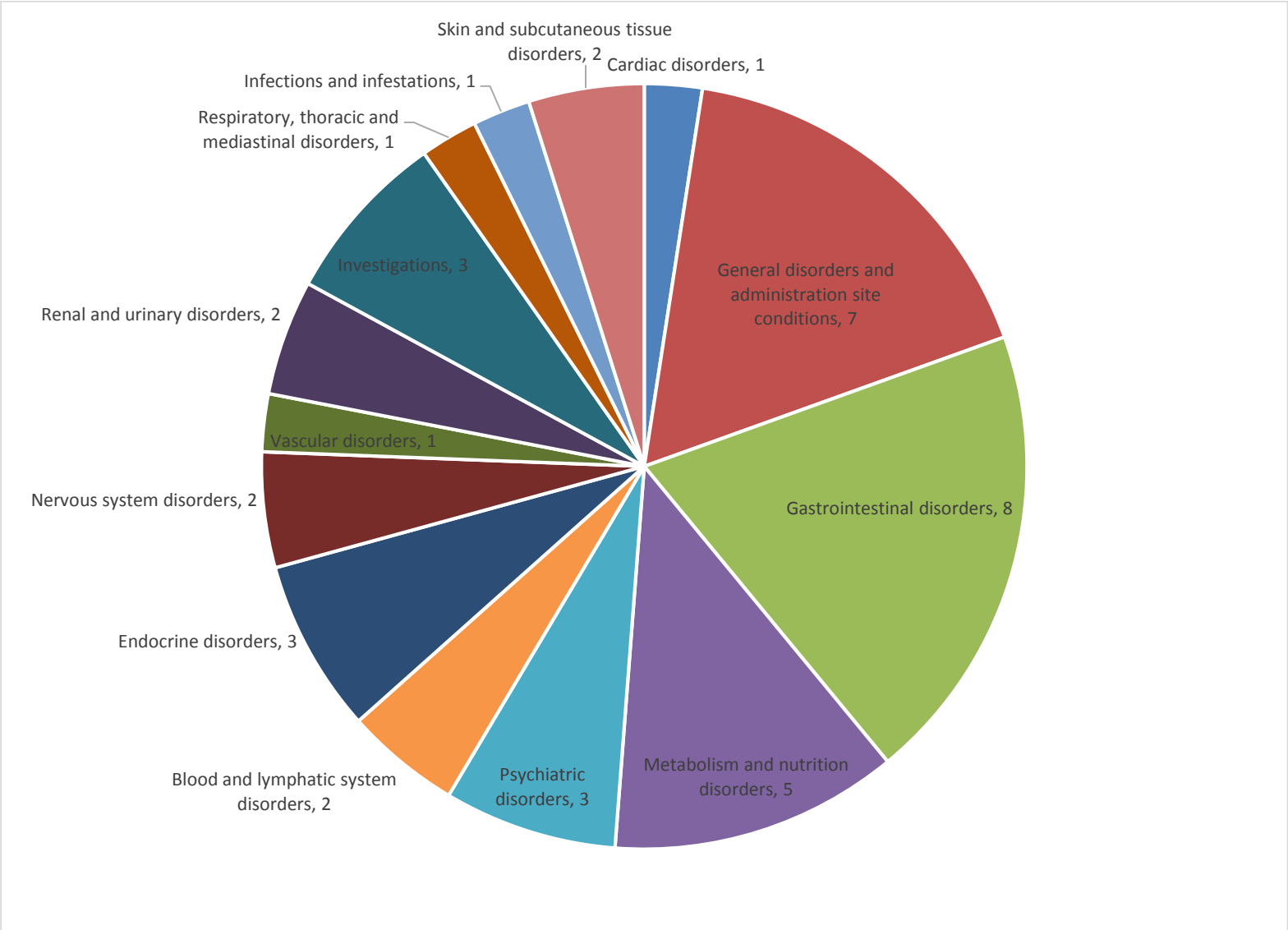


Figure 10 Reported Reactions by System Organ Class for pembrolizumab



[redacted]

One case of hyperglycaemia was reported with nivolumab but no other reports of diabetes have been received for either nivolumab or ipilimumab.

Other severe ADRs noted were cardiac ADRs (cardiac failure, myocardial ischaemia) reported with pembrolizumab and nivolumab. Adrenal insufficiency (Endocrine disorders SOC) was also reported in association with pembrolizumab.

Comment

A review of the cases indicates a wide range of reactions have been reported to CARM associated with the use of these medicines. A short onset time and severe ADRS were also noted in some cases suggesting a need for monitoring.

Given the mechanism of action of immune checkpoint inhibitors the development of diabetes may not be unexpected from the use of these medicines. [redacted]

Wording with regards to monitoring is present in the data sheets for the immune checkpoint inhibitors currently approved for use in New Zealand.

4.0 DISCUSSION AND CONCLUSIONS

The use of immune checkpoint inhibitors are a relatively new and promising anti-cancer treatment in New Zealand. However due to their mechanism of action, they are also associated with a number of immune-related adverse events. A wide range of immune-related adverse events have been identified in the literature and are also listed in New Zealand and international product information for these medicines (pembrolizumab, ipilimumab, nivolumab and atezolizumab).

Two severe cases reporting the development of diabetes associated with the use of pembrolizumab have been received by CARM. These cases, together with noting that the use of these medicines in New Zealand is relatively new and likely to increase, were the trigger for this review.

This review looked at recent reviews by international regulators, Periodic Benefit Risk Assessment Reports (PBRERs) by the sponsors and New Zealand adverse event reports. In general these indicate that a wide range of immune-related adverse effects are associated with the use of these medicines however short onset times and severe ADRs were also seen. Immune-mediated adverse effects are

also listed in New Zealand product informatio [redacted]. [redacted] The Yervoy (ipilimumab) data sheet does however list other immune-related endocrinopathies such as hypophysitis, hypopituitarism, adrenal insufficiency and hypothyroidism. Diabetes is listed in the data sheets for the other three immune checkpoint inhibitors.

A review of the reports received by CARM show a range of reactions have been reported in association with immune checkpoint inhibitors in New Zealand. Overall, the most reported reactions fall into the 'General disorders and administration site conditions' and the 'Gastrointestinal disorders' SOCs. Disease progression was the most reported reaction in the 'General disorders and administration site conditions' SOC. Other ADRs were fatigue, malaise, chest tightness/pain, fever, peripheral oedema, abnormal gait and generalised weakness. Diarrhoea was the most reported ADR in the 'Gastrointestinal disorders' SOC (5 cases). Other ADRs were nausea, faecal incontinence, abdominal distension, colitis, constipation, ascites and abdominal pain/distension.

In general, New Zealand data sheets appear to include information on the main system organ classes identified from literature and regulatory reviews. [redacted], the data sheets lists all important identified risks that have been identified by the company in PRBERs.

To date, no communication has been published by Medsafe on the use of these medicines and associated immune-related adverse events.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- communication to healthcare professionals or consumers other than MARC's Remarks in Prescriber Update is required
- any other regulatory actions are required.

6.0 ANNEXES

1. Pardoll, 2012
2. CARM Data

7.0 REFERENCES

1. Ministry of Health. *Cancer*. 17 July 2017]; Available from: http://www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/cancer.
2. Cancer Society New Zealand. *What is cancer?* 17 July 2017]; Available from: https://wellington.cancernz.org.nz/cancer-information/other-links/what-is-cancer/.
3. Malhotra, J., S.K. Jabbour, and J. Aisner, *Current state of immunotherapy for non-small cell lung cancer.* Transl Lung Cancer Res, 2017. **6**(2): p. 196-211.
4. Luke, J.J. and P.A. Ott, *PD-1 pathway inhibitors: the next generation of immunotherapy for advanced melanoma.* Oncotarget, 2015. **6**(6): p. 3479-92.
5. Harvey, R.D., *Immunologic and clinical effects of targeting PD-1 in lung cancer.* Clin Pharmacol Ther, 2014. **96**(2): p. 214-23.
6. Pardoll, D.M., *The blockade of immune checkpoints in cancer immunotherapy.* Nat Rev Cancer, 2012. **12**(4): p. 252-64.

7. American Cancer Society. *Immune checkpoint inhibitors to treat cancer*. 23 June 2017]; Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html.

8. Bristol-Myers Squibb (NZ) Limited. *Opdivo Data Sheet*. 2017 21 August 2017]; Available from: http://www.medsafe.govt.nz/profs/Datasheet/o/opdivoinf.pdf.

9. Bristol-Myers Squibb (NZ) Limited. *Yervoy Data Sheet*. 2017 21 August 2017]; Available from: http://www.medsafe.govt.nz/profs/Datasheet/y/yervoyinj.pdf.

10. Merck Sharp and Dohme (New Zealand) Limited. *Keytruda Data Sheet*. 2017 21 August 2017]; Available from: http://www.medsafe.govt.nz/profs/Datasheet/k/Keytruda.pdf.

11. Roche Products (New Zealand) Limited. *Tecentriq Data Sheet*. 2017 21 August 2017]; Available from: http://www.medsafe.govt.nz/profs/Datasheet/t/Tecentriqinf.pdf.

12. National Cancer Institute. *NCI Dictionary of Cancer Terms*. 21 July 2017]; Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=772606.

13. Sznol, M., et al., *Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management.* Cancer Treat Rev, 2017. **58**: p. 70-76.

14. Camacho, L.H., *CTLA-4 blockade with ipilimumab: biology, safety, efficacy, and future considerations.* Cancer Med, 2015. **4**(5): p. 661-72.

15. Tarhini, A., E. Lo, and D.R. Minor, *Releasing the brake on the immune system: ipilimumab in melanoma and other tumors.* Cancer Biother Radiopharm, 2010. **25**(6): p. 601-13.

16. Gonzalez-Rodriguez, E., D. Rodriguez-Abreu, and I.-B. Spanish Group for Cancer, *Immune Checkpoint Inhibitors: Review and Management of Endocrine Adverse Events.* Oncologist, 2016. **21**(7): p. 804-16.

17. UpToDate. *Acute viral encephalitis in children: Clinical manifestations and diagnosis*. 2017 8 August 2017]; Available from: https://www.uptodate.com/contents/acute-viral-encephalitis-in-children-clinical-manifestations-and-diagnosis.

18. UpToDate. *Viral encephalitis in adults*. 2017 8 August 2017]; Available from: https://www.uptodate.com/contents/viral-encephalitis-in-adults.

19. European Medicines Agency. *Tecentriq*. 2017 8 August 2017]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004143/smops/Positive/human_smop_001173.jsp&mid=WC0b01ac058001d127.

20. Medicines and Healthcare products Regulatory Agency. *Nivolumab (Opdivo), pembrolizumab (Keytruda): reports of organ transplant rejection*. Drug Safety Update 2017 27 July 2017 [cited 2017; July 2017:[Available from: www.gov.uk/government/uploads/system/uploads/attachment_data/file/632819/DSU-July_PDF.pdf.

21. European Medicines Agency. *Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting on 6-9 March 2017*. 2017 28 July 2017]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf.

22. European Medicines Agency, *Pharmacovigilance Risk Assessment Committee (PRAC): Minutes of the meeting on 24-27 October 2016.* 2017.

23. European Medicines Agency. *PRAC recommendations on signals: Adopted at the 6-9 March 2017 PRAC meeting*. 2017 28 July 2017]; Available from:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf.

24. Health Canada. *Keytruda (pembrolizumab) - RIsk of Severe Skin Reactions: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis*. 2017 27 July 2017]; Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/62670a-eng.php.

25. Gauci, M.L., et al., *Autoimmune diabetes induced by PD-1 inhibitor-retrospective analysis and pathogenesis: a case report and literature review.* Cancer Immunol Immunother, 2017.

26. Abdel-Wahab, N., M. Shah, and M.E. Suarez-Almazor, *Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports.* PLoS One, 2016. **11**(7): p. e0160221.

27. Cappelli, L.C., et al., *Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab.* Ann Rheum Dis, 2017. **76**(1): p. 43-50.

28. Bertrand, A., et al., *Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis.* BMC Med, 2015. **13**: p. 211.

29. Hughes, J., et al., *Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy.* Diabetes Care, 2015. **38**(4): p. e55-7.

30. Larkin, J., et al., *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(1): p. 23-34.

31. Robert, C., et al., *Pembrolizumab versus Ipilimumab in Advanced Melanoma.* N Engl J Med, 2015. **372**(26): p. 2521-32.