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PRODUCT REVIEW

Tecentriq (atezolizumab) in previously-treated non-small-cell lung cancer

Making Education Easy 2018

Independent expert commentary provided by Dr Laird Cameron

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Having initially completed a BSc majoring in biochemistry, Laird graduated from Otago Medical School in 2003. He undertook his core general medical and oncology training in Wellington.

In 2016 he completed a 2-year clinical fellowship in lung and head & neck malignancies at the Peter MacCallum Cancer Centre in Melbourne, Australia, before commencing work as a medical oncologist in the public and private setting in Auckland. Currently he leads the lung cancer medical oncology team at Auckland DHB, is the NZ representative on the Australasian Lung Trials Group and Chair of the newly formed NZ Lung Special Interest Group.

Tecentriq (atezolizumab) is a humanised, engineered, IgG1 monoclonal antibody targeting programmed death ligand-1 (PD-L1) and thus has a mechanism of action distinct from PD-1 inhibitors. In addition to blocking the PD-L1 and PD-1 interaction, which can reinvigorate suppressed immune cells to eliminate cancer cells, atezolizumab blocks PD-L1 and B7.1 binding, which might further enhance immune responses. Furthermore, direct targeting of PD-L1 leaves the PD-L2 and PD-1 interaction intact and might minimise autoimmunity. The aim of this review is to explain the PD-L1 pathway and its role in the immune response and highlight the mode of action of atezolizumab. Important safety and efficacy data for atezolizumab in previously-treated non-small-cell lung cancer (NSCLC) are described. This publication has been commissioned by Roche Products (New Zealand) Limited.

Background

Lung cancer is the leading cause of cancer-related deaths worldwide[1], and in New Zealand.[2] With the 5-year survival rate in lung cancer patients diagnosed between 2005-2009 at only 10%–20%[3], further necessary advances in the treatment of NSCLC, including immunotherapy have been made over the last decade.

Docetaxel has been the standard-of-care second-line chemotherapy after a platinum doublet, but has significant toxicity issues. More recently pemetrexed is used for non-squamous NSCLC and is better tolerated. The development of immune checkpoint inhibitors as anticancer therapy represents one of the most successful approaches in cancer drug discovery in recent years.[4] Initial survival gains were demonstrated in melanoma with lung cancer evidence following closely. Currently, the two classes of immune checkpoint inhibitors that have been approved in New Zealand for clinical use are (1) inhibitors of either PD-1 or its ligand (PD-L1), or (2) cytotoxic T lymphocyte antigen 4 (CTLA-4). Only the former are approved for treating lung cancer.

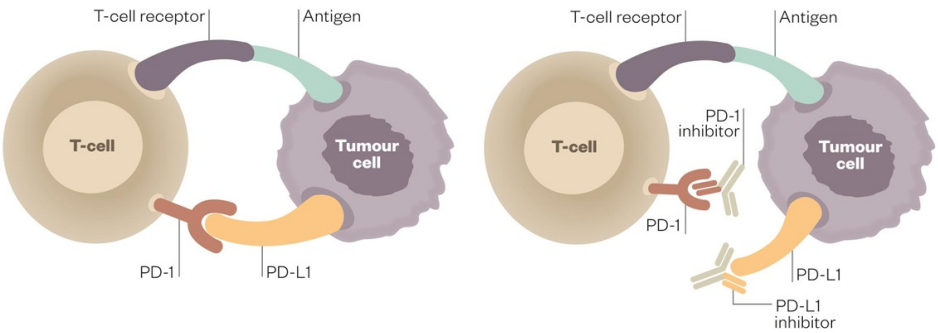
Immune checkpoint inhibition refresher

Cancer cells must develop immune resistance mechanisms to avoid recognition by the host immune system that allows them to grow.[5] One mechanism used by cancer cells involves immune inhibitory pathways or immune checkpoints.[6] CTLA-4 and PD-1 are two important immune-checkpoint receptors involved in the immune process.[6] CTLA-4 predominantly regulates T-cell activation and PD-1 predominantly regulates T-cell activity in the effector phase within tissue and tumours.[6]

The PD-L1/PD-1 pathway

PD-1 is a checkpoint molecule that is expressed by activated T-cells following chronic infections or tumours.[7] PD-1 is thought to act primarily in peripheral tissues where it limits T-cell activity during an inflammatory response to infection limiting autoimmunity.[6] In contrast to the early acting CTLA-4, PD-1 is thought to affect the T-cell response at a later stage.[7] When PD-1 binds to its ligand (PD-L1) the T-cell receives an inhibitory signal which then blocks the anti-tumour immune response (Figure 1).[6-8] 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.[7,8]

Figure 1. The PD-L1/PD-1 pathway[8]



Deactivated T-cell: When PD-1 on the T-cell binds to PD-L1 on the tumour cell, the T-cell becomes deactivated, allowing the cancer cell to evade immune attack.

Activated T-cell: Inhibitors of PD-L1 and PD-1 can prevent the tumour cell from binding to PD-1, enabling the T-cell to remain active.

Abbreviations: PD-1 = programmed death 1; PD-L1 = programmed death ligand 1

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The role of the PD-L1/PD-1 pathway in maintaining immune homeostasis

Under normal conditions, the PD-L1/PD-1 pathway plays an important role in maintaining immune homeostasis.[9] PD-L1 is broadly expressed in multiple tissue types, including haematopoietic, endothelial, and epithelial cells.[9,10] PD-L1 binds to two receptors: B7.1 and PD-1.[9,11] B7.1 is primarily expressed on dendritic cells and to a lesser extent on T-cells[12] while PD-1 is expressed primarily on activated T-cells.[9] When PD-L1 is bound to its receptors, cytotoxic T-cell activity is downregulated, thereby protecting normal cells from autoimmunity.

PD-L2 is an alternative ligand for PD-1.[13] PD-L2 binds primarily to PD-1.[13] PD-L2 has restricted expression on dendritic and epithelial cells in normal tissues such as the lung.[13] Although the exact role of PD-L2 is unclear, the interaction of PD-L2 and PD-1 may potentially preserve immune homeostasis in normal tissues.[13]

Targeting the PD-L1/PD-1 pathway in cancer

In cancer, the PD-L1/PD-1 pathway can downregulate the anticancer immune response by inhibiting cytotoxic T-cell activity in the tumour microenvironment and preventing the priming and activation of new T-cells in the lymph node (Table 1).[10,14] PD-L1 suppresses anticancer immunity through the binding of two different receptors, PD-1 and B7.1.[15,16]

Table 1. The PD-L1/PD-1 pathway in cancer[10,13,17-19]

		Binds to	Mainly expressed in	Importance in the anticancer immune response
PD-1		PD-L1 and PD-L2	• Activated T cells • Monocytes • Dendritic cells	Inactivates cytotoxic T cells during cancer cell recognition following PD-L1 binding
PD-L1		PD-1 and B7.1	• Dendritic cells • Macrophages • T and B cells • Tumour cells	Inhibits priming and activation of T cells via B7.1, and inactivates T cells via PD-1 during cancer cell recognition
PD-L2		PD-1	• Epithelial cells • Myeloid dendritic cells • Macrophages • Mast cells	The exact role of PD-L2 in anti-cancer immunity is unclear; the interaction of PD-L2 and PD-1 may preserve immune homeostasis in normal tissues
B7.1		CTLA-4, CD28 and PD-L1	• Dendritic cells • Monocytes	Modulates priming and activation of T cells via CD28 (stimulation) or CTLA-4 and PD-L1 (suppression)

Abbreviations: CD = cluster of differentiation; CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2

Mechanism of action: PD-L1 inhibitors vs PD-1 inhibitors

Atezolizumab is a monoclonal antibody that binds directly to PD-L1.[20] PD-L1 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.[18] Tumour regression or non-progression may result from the restored anti-tumour responses produced by these anti-cancer agents.[7] Atezolizumab is approved for use in New Zealand for the treatment of NSCLC after previous chemotherapy and urothelial carcinoma[20] but is not currently funded by PHARMAC.

Nivolumab and pembrolizumab, which are also currently available in New Zealand, target PD-1. Nivolumab is indicated for the treatment of NSCLC, metastatic melanoma, renal cell carcinoma, Hodgkin lymphoma and squamous cell carcinoma of the head and neck.[21] Pembrolizumab is indicated for the treatment of NSCLC, metastatic melanoma, Hodgkin lymphoma and urothelial carcinoma.[22] Both these medicines are currently funded by PHARMAC for metastatic melanoma only.

Table 2 below shows the differences between PD-L1 inhibitors versus PD-1 inhibitors in cancer. Both PD-L1 inhibitors and PD-1 inhibitors can reinvigorate suppressed T-cells through blocking the interactions of PD-L1 (on tumour cells and tumour-infiltrating immune cells) in the tumour microenvironment with PD-1.[18]

PD-L1 inhibitors can enhance T-cell priming and activation in the lymph node through blocking the interaction of PD-L1 with B7.1. By blocking PD-L1, B7.1 is available to bind to CD28. B7.1 binding to CD28 provides a co-stimulatory signal to T-cells for priming and activation.[18]

PD-L1 inhibitors also have the ability to preserve immune homeostasis in normal tissue by sparing the interaction of PD-L2 (on normal tissue) with PD-1.[18] Indeed, high expression of PD-L2 was associated with clinical benefit of atezolizumab therapy across distinct cancer types.[23] These data suggest that expression of PD-L2 does not provide a mechanism of immune escape to atezolizumab therapy.[23] In a murine model of asthma, PD-L2 weakened cytokine release from invariant nature killer T-cells and decreased airway hyperreactivity[24] implying a role for PD-L2 in inflammation homeostasis of the lung. PD-L1 Inhibitors do not affect this pathway whereas PD-1 inhibitors could potentially do. Hence there is a pre-clinical rationale for a favourable efficacy and toxicity profile, including less pneumonitis, with PD-L1 inhibitors compared to PD-1 inhibitors.[25]

Table 2. Mechanism of action of PD-L1 inhibitors vs PD-1 inhibitors in cancer

Agents targeting PD-L1/PD-1 axis	Ligand:receptor interaction blocked and potential biological relevance		
	PD-L1:PD-1	PD-L1:B7.1	PD-L2:PD-1
	Reinvigorate suppressed T-cells	Enhance T-cell priming and function	Autoimmune reactions in normal tissue
Anti-PD1 agents (e.g. nivolumab, pembrolizumab)	Yes	No	Yes
Anti-PD-L1 agents (e.g. atezolizumab, durvalumab)	Yes	Yes	No

Abbreviations: PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2

Key trials in metastatic NSCLC

A phase 1 study of atezolizumab monotherapy revealed durable antitumour responses in NSCLC and an association of PD-L1 expression on tumour cells and tumour-infiltrating immune cells with patients who had an objective response.[26,27] This led to the open-label, phase 2 BIRCH trial which evaluated atezolizumab in chemotherapy-naïve as well as previously treated advanced NSCLC patients.[28] Only patients with >5% PD-L1 expression in tumour or tumour-infiltrating immune cells were included in the study. Three cohorts of patients were characterised: chemo-naive patients (Cohort 1), patients who had progressed after one prior platinum therapy (Cohort 2), and patients who had undergone two or more prior chemotherapy regimens (Cohort 3). The primary endpoint, overall response rate, for Cohorts 1, 2, and 3 was 24%, 19%, and 19%, respectively. Outcomes correlated with PD-L1 expression.

In the phase 2, randomised POPLAR study, atezolizumab improved overall survival compared with docetaxel in patients with previously treated NSCLC (12.6 months vs 9.7 months; HR 0.73, 95% CI 0.53-0.99) in the intention-to-treat population.[29] Additionally, results suggested that there are two distinct subpopulations of NSCLC that can be identified through PD-L1 expression on tumour cells and tumour-infiltrating immune cells, with PD-L1 expression independently contributing to overall survival. Eight percent of patients in the atezolizumab group discontinued because of adverse events versus 22% of patients in the docetaxel group. Grade 3-4 adverse events occurred in 11% and 39% of patients, respectively.

OAK is the first phase 3 randomised clinical trial to report results for a PD-L1 inhibitor.[30] In this study, atezolizumab showed a significant and clinically relevant improvement in overall survival compared with docetaxel in patients with advanced stage, previously treated NSCLC, regardless of PD-L1 expression (13.8 months vs 9.6 months; HR 0.73, 95% CI 0.62-0.87).

Patients with high PD-L1 expression (TC3 or IC3 subgroup) derived the greatest benefit from atezolizumab (median overall survival 20.5 months [95% CI 17.5-not evaluable] vs 8.9 months [5.6-11.6]; HR 0.41 [95% CI 0.27-0.64]). TC3 was defined as PD-L1 expression on 50% or more of tumour cells and IC3 was defined as 10% or more of tumour-infiltrating immune cells. The OAK trial demonstrated overall survival improvement in patients with little or no PD-L1 expression (<1% on tumour cells and tumour-infiltrating immune cells). There was a survival benefit of atezolizumab over docetaxel across clinical subgroups, including in patients with squamous and non-squamous disease, in present and previous smokers, and in never smokers, which has been associated with lower mutational heterogeneity and immunogenicity. Adverse events leading to treatment discontinuation occurred in 8% of patients in the atezolizumab group versus 19% of patients in the docetaxel group. Fewer patients had grade 3 or 4 adverse events with atezolizumab (37%) versus docetaxel (54%).

Expert commentary on clinical trials

Internationally, PD-L1 and PD-1 targeted immunotherapy is considered standard of care in most patients with advanced wild-type NSCLC that has progressed after a first-line platinum doublet chemotherapy. This is based on four phase 3 trials that assessed nivolumab (Checkmate017, Checkmate057), pembrolizumab (Keynote010) and atezolizumab (OAK). With the appropriate comparator chemotherapy arm in these trials historically achieving a response rate of approximately 10%, the bar was set low, however the apparent durability of an achieved response with immunotherapy is making a significant impact on survival.

There are no randomised trials directly comparing efficacy or toxicity profiles of these three checkpoint inhibitors and likely never will be. Conclusions rely on cross-trial comparisons and are made more difficult with each checkpoint inhibitor trial having a different assay and threshold for PD-L1 testing.

In the second-line setting, atezolizumab was the first PD-L1 inhibitor to demonstrate better outcomes than chemotherapy. This trial was unique in the inclusion of immune cells to give the PD-L1 score. It included patients with a low PD-L1 score (TC0/IC0). In the intention-to-treat population, an overall survival benefit was gained (HR 0.73) and was exaggerated in the PD-L1 high group (HR 0.41). The overall survival benefit was maintained in the PD-L1 low group (HR 0.75) resulting in atezolizumab gaining Medsafe registration for second-line advanced NSCLC treatment regardless of PD-L1 status. Nivolumab has demonstrated a statistically significant overall survival benefit in the PD-L1 TPS (tumour percentage score) <1% group with squamous (CheckMate017) but not non-squamous (Checkmate057) NSCLC. Lastly, the second-line pembrolizumab trial (Keynote010) excluded patients with a PD-L1 TPS <1%.

On a practical level I would prescribe any of these three anti-PD-L1/PD-1 therapies in the second-line setting, depending on price and access. Technically, atezolizumab has an advantage in demonstrated efficacy regardless of PD-L1 status. Unfortunately, despite Medsafe approvals, there is no immunotherapy agent funded to treat lung cancer in New Zealand currently.

Safety and tolerability

A 2017 review of the safety of atezolizumab in the second-line treatment of advanced NSCLC found that the most common adverse events of any grade were fatigue (26.8%), decreased appetite (23.5%), cough (23.2%), asthenia (19%), dyspnoea (19%), nausea (17.7%), pyrexia (17.7%), constipation (17.6%), diarrhoea (15.4%) and arthralgia (12%).[31]

Immune-related adverse events

PD-L1 and PD-1 inhibitors block immune checkpoint receptors and can disrupt normal mechanisms of immune tolerance, leading to increased immune activation in normal tissue.[32] The outcome is profuse unregulated activation of T-cells causing immune-related adverse events with these agents,[32] that differ from the typical adverse events seen with chemotherapeutic agents.[33] The exact pathophysiology underlying immune-related adverse events is unclear but is thought to be related to the role that immune checkpoints play in maintaining immunologic homeostasis.[34] While any organ system can be affected, immune-related adverse events most often involve the gastrointestinal tract, endocrine glands, skin, and liver.[34] Less commonly, the central nervous system and cardiovascular, pulmonary, renal, musculoskeletal, and haematologic systems are affected.[34] The wide range of potential immune-related adverse events requires multidisciplinary, collaborative management by providers across the clinical spectrum. Immune-related adverse events described with atezolizumab treatment are shown in Table 3.

Pneumonitis is an important autoimmune toxicity associated with the use of PD-L1 and PD-1 inhibitors, resulting in significant morbidity and mortality, often resulting in discontinuation of therapy.[35,36] Previous studies have demonstrated a rate of pneumonitis of approximately 4% in patients with NSCLC receiving such therapy, higher than in patients with other types of tumours.[37] In a meta-analysis of all published clinical trials of PD-L1 and PD-1 inhibitor therapy for patients with NSCLC, the overall incidence of all grade pneumonitis was significantly lower in the PD-L1 inhibitor group (1.3%) compared with the PD-1 inhibitor group (3.6%; P=0.001).[32] Grade ≥3 pneumonitis incidence was also significantly lower with PD-L1 inhibitors (0.4% vs 1.1%; P=0.02). Pneumonitis was significantly more common in treatment naive patients compared with previously treated patients.

Table 3: Immune-related adverse events with atezolizumab treatment[20]

N=2160	All grades (%)
Hypothyroidism	4.7
Hyperthyroidism	1.7
Pneumonitis	3.1*
Colitis	1.1
Hepatitis	0.3
Hypophysitis	<0.1
Diabetes mellitus	0.3

* One fatal event.

Expert commentary on safety and tolerability

Experience in the clinic is that day-to-day checkpoint inhibitors are better tolerated than chemotherapy. The majority of side effects are low grade including fatigue, anorexia, rash, itch and musculoskeletal symptoms. However, there is the rare but serious incidence of immune-related adverse events. An autoimmune effect on various organs and body systems can occur at any point in the treatment course including after ceasing therapy. Although high grade events occur in less than 5% of cases, common examples of immune-related adverse events include endocrinopathies (most often asymptomatic changes in thyroid levels), colitis and pneumonitis. Less common events such as encephalitis, nephritis, uveitis, neuropathies, type I diabetes mellitus and pancreatitis can also occur. Communication across specialties including the primary care setting is important. These medications are not chemotherapy and have a very different toxicity profile. Recognition of autoimmune side effects is key to prompt appropriate supportive treatment that often requires early, high dose steroids tapered over a long period.

There is a rationale for drugs targeting PD-L1 to have a lower rate of pneumonitis by preserving the PD-1/PD-L2 interaction. Although a lower rate has been reported in a meta-analysis, pneumonitis still occurs on PD-L1 inhibitors including a reported death due to pneumonitis with atezolizumab. Clinical trials excluded patients with pre-existing pneumonitis and risk factors for who might specifically be at higher risk of pneumonitis are not clear.

TAKE-HOME MESSAGES

- Immune checkpoints, such as the PD-L1 pathway, are regulatory pathways in the immune system that modulate the immune response.[6-8]
- Tumours upregulate PD-L1 expression as a means to evade the host immune response by:
  - Inhibiting cytotoxic T-cell activity in the tumour microenvironment.[14]
  - Preventing the priming and activation of new T-cells in the lymph node.[10]
- Atezolizumab is a humanised, engineered, IgG1 monoclonal antibody that directly and selectively targets human PD-L1.[20]
  - Atezolizumab can reinvigorate suppressed T-cells to kill cancer cells in the tumour microenvironment through blocking the interactions of PD-L1 with PD-1.[18]
  - Atezolizumab can enhance T-cell priming and activation in the lymph node through blocking the interaction of PD-L1 with B7.1.[18]
  - Atezolizumab can preserve immune homeostasis in normal tissue by sparing the interaction of PD-L2 with PD-1.[18]
- In NSCLC, targeting of PD-L1 is associated with a significantly lower incidence of pneumonitis than targeting of PD-1.[32]
- Targeting of PD-L1 with atezolizumab results in a clinically relevant improvement of overall survival as well as a favourable safety profile compared with docetaxel in patients with previously treated NSCLC, regardless of PD-L1 expression or histology.[30]

EXPERT CONCLUDING COMMENTS

Atezolizumab was FDA approved as a second-line treatment for NSCLC in October 2016. Since then, 11 more targeted and immunotherapies have gained FDA approval to treat lung cancer.[38] This reflects the rapidly evolving field of lung cancer treatment that will make an impact on dismal outcomes for this tumour type, depending on access and funding. Of the 11 FDA approved treatments, four have Medsafe approval and none are publicly funded in New Zealand.

Checkpoint inhibitors targeting the PD-1/PD-L1 interaction have changed the landscape of treating advanced lung cancer. In the second-line setting, atezolizumab, pembrolizumab and nivolumab are better tolerated and more effective than standard chemotherapy. Lung cancer Immunotherapy research has since focussed on the first-line metastatic setting, earlier stage NSCLC, combination therapies, biomarkers other than PD-L1 and thoracic cancers other than NSCLC such as small cell lung cancer and mesothelioma.

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Tecentriq® (atezolizumab) Abridged Prescribing Information

Tecentriq (atezolizumab, 1200 mg concentrate for solution for infusion) is a **Prescription Medicine** for the treatment of: adult patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy; adult patients with locally advanced or metastatic urothelial carcinoma who are considered cisplation ineligible, or have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. **Dose and Method of Administration:** Recommended dosage is 1200 mg by IV infusion every three weeks. Please see Data Sheet for further information. **Contraindications:** Hypersensitivity to atezolizumab or to any excipient. **Special warnings and precautions for use:** See Data Sheet for dose modification and treatment advice for the following immune-releated events. ***Immune-related pneumonitis:*** Monitor for signs and symptoms of pneumonitis. Withhold Tecentriq for grade 2; permanently discontinue for Grade 3 or 4 pneumonitis. ***Immune-related hepatitis:*** Monitor for signs and symptoms of hepatitis. Monitor AST, ALT and bilirubin prior to and periodically during treatment. Appropriate management of patients with abnormal LFTs at baseline should be considered. Withhold Tecentriq for persistent grade 2; permanently discontinue for grade 3 or 4 events. ***Immune-related colitis:*** Monitor for signs and symptoms of colitis. Withhold Tecentriq for Grade 2 or 3 diarrhoea or symptomatic colitis; permanently discontinue for grade 4 diarrhoea or colitis. ***Immune-related endocrinopathies:*** Monitor for clinical signs and symptoms of endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus. Monitor thyroid function prior to and periodically during treatment. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered. Withhold Tecentriq for grade 2 or 3; permanently discontinue for grade 4 hypophysitis. Withhold Tecentriq for grade 3 or 4 type 1 diabetes mellitus. Withhold Tecentriq for symptomatic hypothyroidism, hyperthyroidism or adrenal insufficiency. ***Immune-related meningoencephalitis:*** Monitor for clinical signs and symptoms of meningitis or encephalitis. Permanently discontinue treatment for any grade of meningitis or encephalitis. ***Immune-related neuropathies:*** Monitor for symptoms of motor and sensory neuropathy, including myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Permanently discontinue treatment for any grade of these events. ***Immune-related pancreatitis:*** Closely monitor for signs and symptoms suggestive of acute pancreatitis. Withhold Tecentriq for grade 3 or 4 serum amylase or lipase levels increased or grade 2 or 3 pancreatitis. Permanently discontinue for grade 4, or any grade of recurrent pancreatitis. ***Immune-related myocarditis:*** Monitor for signs and symptoms of myocarditis. Withhold Tecentriq for grade 2; permanently discontinue for grade 3 or 4 myocarditis. ***Infusion-related reactions (IRRs):*** Reduce infusion rate or interrupt infusion for grade 1 or 2 IRRs. Tecentriq may be continued with close monitoring; consider premedication with antipyretic and antihistamines. Permanently discontinue treatment for grade 3 or 4 IRRs. ***Patients with autoimmune disease:*** Patients with autoimmune disease were excluded from clinical trials; use with caution after assessment of the potential risk versus benefit. ***Renal impairment:*** No dose adjustment required. ***Hepatic impairment:*** No dose adjustment required for mild impairment. No data in moderate or severe impairment. ***Use in the elderly:*** No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients. ***Use in pregnancy – Category D:*** Tecentriq poses a risk to the Tecentriq 170901 2 human fetus, including embryo lethality. Pregnant women should be advised of the potential risk to the fetus. Women of childbearing potential should use highly effective contraception during treatment and for at least 5 months after the last dose. Safety during labour and delivery has not been established. ***Breastfeeding:*** Either discontinue breastfeeding or discontinue Tecentriq. ***Fertility:*** Tecentriq may impair fertility in females of reproductive potential while receiving treatment.

Undesirable effects: See Data Sheet for full list. Fatal cases of pneumonitis and hepatitis have been observed. ***Blood and lymphatic system:*** thrombocytopenia. ***Cardiac disorders:*** myocarditis. ***Endocrine:*** hypothyroidism; hyperthyroidism; adrenal insufficiency; hypophysitis; diabetes mellitus. ***Gastrointestinal:*** diarrhoea; dysphagia; colitis; nausea; vomiting; abdominal pain; pancreatitis; amylase increased; lipase increased. ***General:*** chills; fatigue; asthenia; influenza-like illness; pyrexia; infusion-related reactions. ***Hepatobiliary:*** ALT increased; AST increased; hepatitis. ***Immune system:*** hypersensitivity. ***Metabolism and nutrition:*** decreased appetite; hypokalaemia; hyponatraemia. ***Musculoskeletal and connective tissue:*** arthralgia; musculoskeletal. ***Nervous system:*** Guillain-Barré syndrome; non-infective encephalitis; non-infective meningitis; myasthenic syndrome. ***Respiratory, thoracic and mediastinal:*** dyspnoea; hypoxia; nasal congestion; pneumonitis (incl. bronchiolitis, interstitial lung disease). ***Skin and subcutaneous tissue:*** pruritus; rash (incl. skin exfoliation, skin ulcer, skin toxicity, palmar-plantar erythrodysaesthesia syndrome, toxic skin eruption, folliculitis, furuncle). ***Vascular:*** hypotension.

Tecentriq is not a PHARMAC-funded medicine.

Before prescribing, please review the Tecentriq Data Sheet available at www.medsafe.govt.nz. API based on Data Sheet 25.08.2017.
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