Medicines Adverse Reactions Committee

Meeting date	**3 December 2020**	Agenda item	3.2.3
Title	**HER2- and CD receptor-targeted monoclonal antibodies and the risk of interstitial lung disease**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Rituximab	Mabthera	Roche Products (NZ) Ltd
	Rixmyo	Novartis New Zealand Ltd
Daratumumab	Darzalex	Janssen-Cilag (New Zealand) Ltd
Obinutuzumab	Gazvya	Roche Products (NZ) Ltd
Inotuzumab ozogamicin	Besponsa	Pfizer New Zealand Limited
Trastuzumab	Herceptin	Roche Products (NZ) Ltd
	Herzuma	Celltrion Healthcare New Zealand Limited
	Trazimera	Pfizer New Zealand Limited
Trastuzumab emtansine	Kadcyla	Roche Products (NZ) Ltd
Pertuzumab	Perjeta	Roche Products (NZ) Ltd

Funding	Rituximab, obinutuzumab, pertuzumab, trastuzumab and trastuzumab emtansine are funded, subject to special authority criteria. Daratumumab and inotuzumab ozogamicin are not currently funded.
Previous MARC meetings	Immune checkpoint inhibitors (atezolizumab, ipilimumab, nivolumab and pembrolizumab) have been discussed previously at the following meeting: – 171st Meeting — 14 September 2017 Review of immune checkpoint inhibitors in the NZ context
Prescriber Update	Spotlight on Pembrolizumab (Keytruda). *Prescriber Update* 39(3): 34–35. September 2018. Medicine-induced Lung Disease. *Prescriber Update* 37(2): 24-26. June 2016.
Schedule	Prescription medicine
Advice sought	**The Committee is asked to advise whether:** – The companies should be asked to assess the risk of interstitial lung disease in Periodic Benefit-Risk Evaluation Reports (PBRERs) for pertuzumab, obinutuzumab and daratumumab – Any data sheet updates should be requested, for example, listing interstitial lung disease in the pertuzumab data sheet – Any other regulatory action is required.

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1.0 PURPOSE

Medsafe was informed by the Centre for Adverse Reactions Monitoring (CARM) of a report of severe, life-threatening interstitial pneumonitis in a patient who received treatment for metastatic melanoma with pembrolizumab (Keytruda). Reports of interstitial lung disease relating to rituximab and trastuzumab have also been received.

The data sheets for immune checkpoint inhibitors (atezolizumab, ipilimumab, nivolumab and pembrolizumab) have been reviewed and contain information on the risk of pneumonitis. Cetuximab (an EGFR-targeted monoclonal antibody), trastuzumab and trastuzumab emtansine (HER2-targeted monoclonal antibodies) and rituximab (a CD20-targeted monoclonal antibody) also have this information in the data sheet.

The possibility of an association of interstitial lung disease with other HER2-targeted and CD receptor-targeted monoclonal antibodies used in the context of oncology is considered in this report.

The purpose of this report is to seek advice on whether the risk of interstitial lung disease should be evaluated in PSURs for any of the medicines of interest, and whether any data sheet updates or other regulatory actions are required.

2.0 BACKGROUND

2.1 The immune system

The immune system recognises and eliminates potentially harmful or abnormal cells and molecules. The immune system can be divided into the innate response and the adaptive response, although the two are interlinked. The innate immune system comprises physical and chemical barriers (eg, skin, stomach acid) as well as immune components (eg, neutrophils, complement) which provide rapid, non-specific defence without prior exposure to the foreign cell or molecule. The adaptive response consists of T-cells and B-cells, which recognise antigens (any molecule or part of a molecule that can stimulate an immune response) and mount a targeted immune response [1].

2.1.1 Immune-mediated mechanisms

The following immune recognition pathways, comprising elements of both innate and adaptive immunity, are thought to be involved in the mechanism of action of some of the monoclonal antibodies discussed in this report.

Antibody-dependent cellular cytotoxicity

Antibody-dependent cellular cytotoxicity (ADCC) involves recognition of the antibody-coated target cell by effector cells. Effector cells are activated cells that defend the body in an immune response (eg, natural killer cells, monocytes, macrophages, T cells). Upon recognition of the antibody-coated target cell, effector cells release cytotoxic substances, resulting in death of the target cell (see Figure 1) [2, 3].

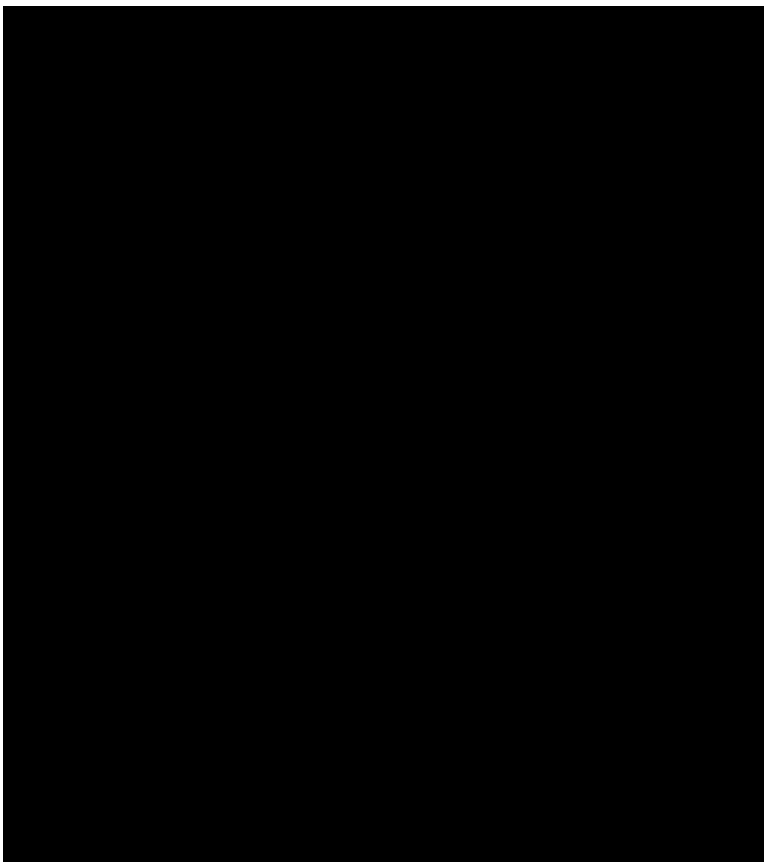
Figure 1: [redacted]

Complement-dependent cytotoxicity

The complement system is a part of the immune system consisting of more than 30 proteins which, once activated, causes chain reactions resulting in elimination of infected cells, foreign and particles and inflammation of surrounding tissue [4].

In the context of monoclonal antibody therapy, complement-dependent cellular cytotoxicity (CDC) involves activation of the classical complement pathway by complement component C1 recognition of antibody bound to antigen on the surface of the target cell. A complex cascade of reactions ensues, culminating in the formation of the membrane attack complex (MAC) which causes cell lysis (see Figure 2) [5].

Figure 2: [redacted]



Antibody-dependent phagocytosis

Phagocytes are a type of cell that has the ability to ingest, and sometimes digest, foreign particles [7]. Antibody-dependent phagocytosis (ADCP) involves recognition of antibody-coated target cells by phagocytes, induction of signalling cascade in the phagocyte, and engulfment and destruction of the target cell (see Figure 3) [8].

Figure 3: [redacted]

Direct apoptosis

Apoptosis is a mechanism that causes cells to self-destruct when stimulated by a trigger such as cellular injury [10]. In the context of rituximab therapy, direct induction apoptosis is thought to result from CD20 crosslinking by antibodies, although this may not contribute significantly to the therapeutic action *in vivo* [11].

2.2 Monoclonal antibodies

Monoclonal antibodies are antibodies produced from a single B-cell clone, with specificity for a target antigen. Possible targets include cell surface antigens, plasma proteins or medicines and infectious organisms [12].

The medicines discussed in this report are mainly used for the treatment of specific cancers, and the targets are proteins that are expressed on the surface of cancer cells. The mechanisms of action vary between the medicines, but in general there are two principles for the activity of monoclonal antibodies that target cell surface antigens:

- The antibody 'blocks' a specific receptor on the target cell, interfering with the receptor function and prevents proliferation or survival.
- Binding of the antibody to the protein triggers recruitment of immune cells such as complement proteins, phagocytes, or natural killer (NK) cells, resulting in immune-mediated cell death [12].

Rituximab, daratumumab and obinutuzumab are monoclonal antibodies that target specific cluster of differentiation (CD) proteins on the surface of normal and malignant lymphocytes. The mechanism of cell destruction is mainly immune-mediated. Inotuzumab ozogamicin also targets a CD protein, but has a different mechanism of cell destruction, as discussed below. [12-15].

Trastuzumab, trastuzumab emtansine and pertuzumab are monoclonal antibodies that target human epidermal growth factor receptor 2 (HER2) protein, particularly on the surface of malignant cells that

overexpress HER2. The mechanism of cell death involves disruption of receptor function, as well as immune-mediated destruction [12, 16, 17].

2.2.1 Rituximab

Rituximab (eg, Mabthera) targets the CD20 antigen on the surface of B lymphocytes. When it binds to CD20, it causes cell death via complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and apoptosis [15].

Rituximab is indicated as monotherapy and/or in combination therapy for CD20 positive B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia (CLL), severe rheumatoid arthritis, granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). The full indications are listed in the data sheet [15].

2.2.2 Daratumumab

Daratumumab targets the CD38 antigen on plasma cells. When it binds to CD38 it is thought to trigger cell death mainly via complement-dependent cytotoxicity (CDC), antibody-dependent cell mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) [18].

Daratumumab (Darzalex) is indicated as monotherapy or in combination therapy for multiple myeloma. The full indications are listed in the data sheet [18].

2.2.3 Inotuzumab ozogamicin

Inotuzumab ozogamicin is comprised of three components:

- inotuzumab, a monoclonal antibody that targets CD22
- N-acetyl-gamma-calicheamicin, a cytotoxic substance that causes double-strand DNA breaks
- an acid cleavable linker that attaches inotuzumab and N-acetyl-gamma-calicheamicin [13].

The inotuzumab component of inotuzumab ozogamicin binds to the CD22 antigen on the surface of precursor (immature) B-cells. The medicine is then internalised (let into the cell), the linker is cleaved, and the released N-acetyl-gamma-calicheamicin dimethylhydrazide component causes double-strand DNA breaks and subsequent cell death via apoptosis [13]. The monoclonal antibody component without the cytotoxic component does not have anti-tumour activity [19].

Inotuzumab ozogamicin (Besponsa) is indicated for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL) [13].

Comments: Unlike the other medicines of interest, the mechanism of cell destruction relies on internalisation of the cytotoxic component and is not related to immune-mediated pathways that may be implicated in development of interstitial lung disease with monoclonal antibody therapy (see section 2.2.4). Therefore, no recommendation has been sought regarding inotuzumab ozogamicin.

2.2.4 Obinutuzumab

Obinutuzumab targets the CD20 antigen on the surface of precursor and mature B lymphocytes. It is thought to trigger cell death via antibody dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and, to a lesser degree, complement dependent cytotoxicity (CDC) [14].

Obinutuzumab (Gazyva) is indicated in combination therapy and monotherapy for chronic lymphocytic leukaemia (CLL), advanced follicular lymphoma and indolent non-Hodgkin lymphoma (iNHL). The full indications are listed in the data sheet [14].

2.2.5 Trastuzumab and trastuzumab emtansine

Trastuzumab (Herceptin) targets the HER2 protein on the surface of cells. Binding to HER2 is thought to interrupt cellular processes mediated by HER2, and also trigger cell death via antibody-dependent cell-mediated cytotoxicity (ADCC), which occurs to a greater extent in cells that over-express HER2 [16, 20].

Trastuzumab emtansine (Kadcyla) consists of two components: trastuzumab, a monoclonal antibody; and DM1, a cytotoxic agent. Like trastuzumab, trastuzumab emtansine interrupts cellular processes and triggers antibody-dependent cell-mediated cytotoxicity (ADCC), but is also internalised and releases DM1, which inhibits tubulin degradation leading to apoptotic cell death [20].

Trastuzumab (Herceptin) is indicated as monotherapy or in combination therapy for HER2 positive breast cancer and HER2 positive advanced gastric cancer. The full indications are listed in the data sheet [16].

Trastuzumab emtansine (Kadcyla) is indicated as monotherapy or in combination therapy for HER2 positive breast cancer. The full indications are listed in the data sheet [20].

2.2.6 Pertuzumab

Pertuzumab (Perjeta) targets the HER2 protein on the surface of cells. Binding to HER2 is thought to trigger cell death by interrupting cellular processes mediated by HER2 and via antibody-dependent cell-mediated cytotoxicity (ADCC) [17].

Pertuzumab is indicated in combination therapy for HER2 positive breast cancer. The full indications are listed in the data sheet [17].

Comments: While the mechanisms of cell destruction vary between the medicines, with the exception of inotuzumab ozogamicin, they all utilise immune-mediated pathways such as ADCC and CDC to some extent. This may have a role in the development of interstitial lung disease (see section 2.3.4).

2.3 Drug-induced interstitial lung disease

Interstitial lung disease (ILD) is a heterogeneous group of diseases that cause inflammation and fibrosis (damage and scarring) of the lung tissue. Many medicines have been implicated in drug-induced interstitial lung disease (DILD) including antimicrobial agents (eg, nitrofurantoin), anti-inflammatory medicines (eg, aspirin), biological medicines (eg, rituximab), cardiovascular medicines (eg, amiodarone), chemotherapy medicines (eg, paclitaxel) and others [21].

The incidence of DILD is unclear and varies from medicine to medicine [22].

2.3.1 Signs and symptoms

Symptoms are usually non-specific and include dyspnoea, cough, and fever. Respiratory crackles and digital clubbing (an abnormal rounding of the nails) can also be seen [21].

Possible risk factors for DILD include increasing age, underlying lung disease or other disease characteristics, concomitant or prior treatment with medicines with known pulmonary toxicity or radiation therapy, smoking, genetic predisposition, dose, male sex, higher alcohol consumption, renal dysfunction and diabetes [22].

Findings on computerised tomography (CT) scan are most commonly a hazy pattern known as ground glass opacification, with or without solid white areas known as consolidation (indicating congestion of small airways). CT features are not specific to a certain medicine, and a given medicine can produce a variety of patterns [22].

DILD can produce virtually all histological patterns (seen under a microscope) of interstitial lung disease. None are specific for DILD [22].

Pulmonary function tests can show decrease in diffusing capacity (how well the lung can transfer gases between air in the lung and red blood cells) and forced vital capacity (how much air can be blown out after a deep breath). However pulmonary function tests lack specificity for DILD [22].

Arterial blood gas may show low oxygen levels at rest. In mild disease, this may only occur upon exertion [21].

Bronchoalveolar lavage (fluid is that introduced into the lung airways then collected for examination) can show increases in white blood cells such lymphocytes, neutrophils, eosinophils, or a mixture, but these patterns are not specific for DILD [22].

2.3.2 Diagnosis

Diagnosis is mainly by exclusion of other causes. Recognition of DILD is difficult because the clinical, radiological, and histological findings are nonspecific. The onset is also unpredictable. The relationship between ILD and a suspect medicine is hard to recognise and confirm, especially where multiple drugs are being used. Knowledge of the patient's baseline pulmonary status is important for separation of drug-induced injury from underlying disease [21, 22].

The diagnosis of DILD is usually based on:

- Clinical, physiological and radiological findings consistent with ILD
- A temporal relationship between onset of symptoms and drug exposure
- Absence of another more likely cause (eg, infection, pulmonary oedema, radiation-induced lung injury, progression of the underlying disease)
- Improvement upon withdrawal of the suspected causative agent with or without corticosteroid therapy and, in some cases, deterioration upon re-challenge[22].

Below are international criteria used in clinical trials for grading the severity of DILD.

Table 1: Grading of drug-induced interstitial lung disease (DILD) based on the National Cancer Institute Common Terminology Criteria for Adverse Events [22].

Grade 1 (mild)	Asymptomatic, radiographic findings only
Grade 2 (moderate)	Symptomatic, not interfering with activities of daily living
Grade 3 (severe)	Symptomatic, interfering with activities of daily living or oxygen indicated
Grade 4 (life-threatening or disabling)	Life-threatening, or ventilator support required
Grade 5 (fatal)	

2.3.3 Management and prognosis

Management of DILD consists of withdrawal of causative medicine, treatment with glucocorticoids and supportive treatment (eg, supplemental oxygen) [21].

DILD can result in irreversible lung injury or death and early recognition is therefore important. DILD mortality is often due to respiratory failure, multiorgan failure, progression of the primary underlying disease or infection secondary to glucocorticoid therapy. A recent literature review found that in the context of oncology, reported mortality ranged from 14 to 51.3% [22].

2.3.4 Proposed mechanisms

The mechanism of DILD is unclear, but the following general mechanisms have been proposed for various classes of antineoplastic medicines:

- Direct lung injury resulting in release of cytokines and recruitment of inflammatory cells
- Systemic cytokine release resulting in endothelial dysfunction, capillary leak syndrome, and oedema (eg, gemcitabine)
- Cell-mediated lung injury due to activation of lymphocytes and alveolar macrophages
- Oxidative injury from free oxygen radicals (eg, bleomycin)

- Unintended dysregulation of the immune system and T-cell activation caused by immune-checkpoint blockade (eg, pembrolizumab)
- Targeting of EGFR by certain medicines may impair alveolar repair mechanisms (eg, cetuximab)
- Subclinical cumulative radiation injury becoming apparent when another medicine causes injury at a later date
- The medicine acts as antigen or hapten (a small molecule that elicits an immune response only when attached to a large carrier such as a protein) leading to immune damage due to drug-specific antibodies or T cells
- Inflammatory response triggered by deposition of antigen-antibody complexes [21, 23].

The following mechanisms have been proposed for rituximab-induced ILD specifically:

- Complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and TNF-α release and resultant recruitment of inflammatory cells [24-26]
- T cell activation resulting in vascular and alveolar damage [24]
- Interaction of rituximab with CD20-positive T cells or cross-reactivity between lung and tumoral antigens, resulting in generation of self-reactive T cells [24]
- Hypersensitivity reaction to the antibody [27].

Comments: None of the literature posited a mechanism for trastuzumab-induced ILD. The proposed explanations for established relationships between ILD and monoclonal antibodies such as rituximab and pembrolizumab are related to the immune-mediated mechanisms of action. These immune-mediated pathways are also utilised by the other monoclonal antibodies discussed (pertuzumab, obinutuzumab and daratumumab) and may contribute to a risk of interstitial lung disease. However, a relationship between pertuzumab, obinutuzumab and daratumumab and ILD does not currently appear to be documented in the literature.

2.4 Data sheets

2.4.1 New Zealand data sheets

The text in the 'warnings and precautions' section of the NZ data sheet relating to ILD for the medicines of interest is replicated in the table below, and a tick in the 'undesirable effects' column indicates that 'interstitial lung disease' or 'pneumonitis' is mentioned in that section.

Active (trade name)	Warnings and Precautions	Undesirable effects
Rituximab (Mabthera, Rixmyo)	ILD not included. Discussion of pulmonary events is limited to acute respiratory failure occurring within hours of administration.	✓
Daratumumab (Darzalex)	ILD not included.	x
Inotuzumab ozogamicin (Besponsa)	ILD not included.	x
Obinutuzumab (Gazyva)	ILD not included.	x
Trastuzumab (Herceptin)	Under 'Pulmonary reactions', states, 'Severe pulmonary events leading to death have been reported with the use of Herceptin in the post-marketing setting. These events may occur as part of an infusion-related reaction (see Infusion-related reactions (IRRs)); Hypersensitivity reactions including anaphylaxis or with delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other antineoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Herceptin'.	✓

Active (trade name)	Warnings and Precautions	Undesirable effects
Trastuzumab emtansin (Kadcyla)	Under 'Pulmonary toxicity', states, 'Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with Kadcyla (see section 4.8). Signs and symptoms include dyspnoea, cough, fatigue, and pulmonary infiltrates. It is recommended that treatment with Kadcyla be permanently discontinued in patients who are diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where Kadcyla should be permanently discontinued for ≥ Grade 3 or for Grade 2 not responding to standard treatment (see section 4.2). Patients with dyspnoea at rest due to complications of advanced malignancy, co-morbidities, and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary events'. In the dosage instructions, there is also an instruction in the dose modification table to discontinue treatment in the event of interstitial lung disease.	✓
Pertuzumab (Perjeta)	ILD not included.	x

2.4.2 International prescribing information

The international prescribing information relating to ILD for the medicines of interest is summarised below. A tick in the 'warnings and precautions' or 'undesirable effects' column indicates that 'interstitial lung disease' or 'pneumonitis' is mentioned in that section. The text relating to ILD in the 'warnings and precautions' section of the prescribing information is summarised in the table footnotes.

Active (trade name)	Warnings and precautions section					Undesirable effects section				
	UK	IE	AU	CA	US	UK	IE	AU	CA	US
Daratumumab (Darzalex)	x	x	x	x	x	x	x	x	x	x
Inotuzumab ozogamicin (Besponsa)	x	x	x	x	x	x	x	x	x	x
Obinutuzumab (Gazyva)*	x	x	x	x	x	x	x	x	✓*	x
Rituximab (Mabthera, Rixmyo)	x	x	x	x	x	✓	✓	✓	✓	✓
Pertuzumab (Perjeta)	x	x	x	x	x	✓	✓	✓	✓	x
Trastuzumab (Herceptin)**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Trastuzumab emtansin (Kadcyla)***	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Abbreviations: UK=United Kingdom, IE=Ireland, AU=Australia, US=United States, CA=Canada, ADR=adverse drug reaction, NHL=non-Hodgkin's lymphoma, CLL=chronic lymphocytic leukaemia, ILD=interstitial lung disease.

* The CA information states in post-market ADRs for NHL and CLL, 'ILD, some with fatal outcome, has been reported'.

**The UK, IE and AU prescribing information contain text that is similar to the NZ data sheet, stating that cases of ILD have been reported, with the same risk factors noted. The information states that these events may be associated with an infusion-related reaction or be delayed in onset, and that caution should be exercised in patients with pneumonitis, especially those who are also being treated with taxanes. The CA information is similar to the above, with additional text states that cases of pulmonary fibrosis were characterised by confounding factors including pre-existing lung disease and other chemotherapy, but a causal relationship cannot be excluded. The US information states that interstitial pneumonitis can occur, especially as sequelae to infusion-related reactions, and that patients with pre-existing lung disease appear to have more severe toxicity.

***The UK, IE and AU prescribing information contain text that is the same as the NZ data sheet, stating that cases of ILD have been reported, the medicine should be discontinued in the event of ILD, and that patients with pre-existing dyspnoea at rest may be at increased risk. The CA and US information is also similar to the NZ data sheet, but states the incidence of ILD in each clinical trial (ranging from 0.8-1.1%).

Comments: The New Zealand data sheets are largely consistent with the international prescribing information. However, ILD is listed as a possible ADR for pertuzumab in the UK, Ireland, Australia and Canada, but not in NZ. ILD is also listed as a possible ADR for obinutuzumab in Canada only. The descriptions of the risk of ILD in the NZ trastuzumab and trastuzumab emtansine data sheets are consistent with international prescribing information.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

A search of PubMed for the terms 'drug-induced interstitial lung disease' and 'monoclonal antibodies' generated five results relevant to the medicines of interest. These included a case study of drug-induced interstitial lung disease (DILD) in patients treated with rituximab, a retrospective analysis of pulmonary toxicity in patients treated for lymphoma, two reviews of DILD in patients treated for rheumatoid arthritis, and an analysis of rates of autoimmune disease in patients exposed to biologic medicines.

A search of PubMed for the terms 'drug-induced interstitial lung disease' and 'rituximab' generated one additional broad review article on iatrogenic pulmonary lesions and one case study of interstitial lung disease in a patient with GPA.

A search of PubMed for the terms 'drug-induced interstitial lung disease' and 'trastuzumab' generated one additional review of DILD in patients treated with anti-HER2 therapies (trastuzumab and trastuzumab emtansine), and one case series and one case report relating to trastuzumab and DILD.

A search of PubMed for the terms 'drug-induced interstitial lung disease' and 'daratumumab', 'obinutuzumab', 'inotuzumab' or 'pertuzumab' generated no results.

There were some Japanese articles which were not included above as these were not published in English. Japan has a high rate of reporting of interstitial lung disease as an adverse drug reaction, with one third of literature in a recent systematic review of DILD originating from Japan. The reasons for this are unclear, but may be due to different disease definitions [22].

The most relevant articles are summarised below.

3.1.1 Case studies

The following is a summary of relevant case studies identified in the PubMed search:

- A 65-year-old male developed progressive dry cough and digital clubbing after starting rituximab-CHOP chemotherapy for non-Hodgkin lymphoma. A lung biopsy was consistent with hypersensitivity pneumonitis. The patient subsequently developed a fatal intra-alveolar haemorrhage [24].
- A male treated for granulomatosis with polyangiitis (Wegener's granulomatosis - inflammation of blood vessels) with rituximab, steroids, cyclophosphamide, and plasmapheresis developed pneumonitis two weeks after his second dose of rituximab. He improved upon administration of high-dose corticosteroids [28].
- A 51-year-old female being treated for locally advanced breast cancer developed drug-induced interstitial pneumonitis after 10 weeks of treatment with paclitaxel and trastuzumab. She improved after treatment with steroids [29].
- Three female patients being treated for breast cancer developed interstitial lung disease (ILD) during trastuzumab monotherapy in an adjuvant setting. Prior chemotherapy included epirubicin, cyclophosphamide and docetaxel. All 3 patients improved with discontinuation of trastuzumab and corticosteroid therapy [30].

3.1.2 Lim KH, Yoon HI, Kang YA, et al. 2010

This study [25] aimed to compare the incidence and clinical features of pulmonary complications, including drug-induced interstitial pneumonitis, in patients treated for lymphoma with either cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab plus CHOP (R-CHOP).

A retrospective analysis of Korean lymphoma registry data was carried out for the years 2003 to 2007. A total of 100 patients were included in the study, with 71 in the R-CHOP group and 29 in the CHOP group. The baseline characteristics of the patients were similar across the groups, apart from cancer type, as rituximab is only used for B-cell lymphoma. Therefore, all patients receiving R-CHOP had B-cell non-Hodgkin's lymphoma (NHL), while most patients receiving CHOP had T-cell NHL. Diagnoses of drug-induced interstitial pneumonitis were made on the basis of high-resolution computed tomography (HRCT) findings, pathology results and clinical features.

One patient in the CHOP group (3%) and five patients in the R-CHOP group (7%) were diagnosed with drug-induced interstitial pneumonitis. The authors concluded that it is plausible that rituximab contributed to the higher rate of drug-induced interstitial pneumonitis seen in patients treated with R-CHOP and that clinicians should be vigilant about monitoring for pulmonary toxicity in this patient group.

3.1.3 Hackshaw MD, Danysh HE, Singh J, et al. 2020

This literature review [31] aimed to describe the incidence of ILD patients with HER2-positive metastatic breast cancer (MBC) receiving anti-HER2 therapies. Clinical trials and post-market observational studies were identified from Embase and PubMed.

The 18 articles selected for the review encompassed treatment of 9,886 patients with trastuzumab, lapatinib, trastuzumab emtansine, trastuzumab deruxtecan, or trastuzumab duocarmazine. One study in the review included pertuzumab in combination with trastuzumab and other chemotherapy, although this study reported radiation pneumonitis only. The overall incidence of ILD was found to be 2.4%. The incidence of ILD in individual studies varied from 0% to 21.4%, with higher rates seen in studies where patients were treated concomitantly with other therapies known to be associated with ILD.

The authors concluded that ILD is associated with anti-HER2 therapies and that monitoring for this risk is warranted. Although the mechanism for DILD with these medicines is not discussed, the paper describes DILD as a class effect of anti-HER2 therapy, and noted that other immune-mediated cancer therapies such as immune checkpoint inhibitors and CDK 4/6 inhibitors have been implicated in DILD.

3.1.4 Lioté H, Lioté F, Séroussi B, et al. 2010.

This literature review [27] critically reviews data on the clinical presentations, causality assessments and management strategies of lung diseases possibly related to rituximab. As the review was not specific to ILD, only the data relevant to ILD is discussed here. The relevant data are considered to be the 37 cases grouped as delayed-onset acute lung disease (presenting as acute/subacute hypoxaemic organising pneumonia) and the three cases grouped as late-onset chronic lung disease (presenting as macronodular organising pneumonia).

A systematic review was undertaken of all cases in English or French in PubMed describing ILD as an adverse reaction associated with rituximab therapy for any indication from 1997 to 2008. A quality assessment, relating to presence of valuable data, especially for time to onset, exclusion of other causes, and re-introduction conditions, was applied to the identified cases. Forty-five cases were included in the study, 40 of which can be classified as ILD. Development of ILD occurred around two weeks after the last rituximab infusion in 37 cases, and one to three months after the last infusion in three cases. Of the 15 cases where re-challenge was conducted, 12 gave positive results and 3 were negative with concomitant high dose steroids. There were no further symptoms in nine patients who had chemotherapy restarted without rituximab.

The authors concluded that all cases of interstitial lung disease identified in the review were plausibly attributable to rituximab. The proposed mechanism for acute or subacute lung disease (organising pneumonia) was a hypersensitivity reaction to the potentially immunogenic chimeric anti-CD20

antibody. The proposed mechanism for late-onset organising pneumonia was drug toxicity or immune system restoration.

Comments: The relevant literature found largely reinforces what is already included in the data sheets for rituximab, trastuzumab and trastuzumab emtansine. No literature was found that specifically relates to pertuzumab, inotuzumab ozogamicin, obinutuzumab or daratumumab.

3.2 CARM data

CARM has received four reports of interstitial lung disease relating to rituximab, and one report of interstitial lung disease relating to trastuzumab. The CARM report is provided in Annex 1. Please note that the report also contains cases relating to medicines that are outside of the scope of this report.

4.0 DISCUSSION AND CONCLUSIONS

Interstitial lung disease is a rare but potentially fatal group of lung diseases that have been attributed to a number of monoclonal antibodies used in the treatment of malignant disease, including atezolizumab, ipilimumab, nivolumab, pembrolizumab, cetuximab, rituximab, trastuzumab and trastuzumab emtansine.

There is a plausible biological mechanism for a link between ILD and other monoclonal antibodies such as pertuzumab, obinutuzumab and daratumumab, which utilise similar immune-mediated pathways for their action. However, a relationship between pertuzumab, obinutuzumab and daratumumab and ILD does not currently appear to be documented in the literature.

Inotuzumab ozogamicin appears to have a distinct mechanism of action of cell destruction that is not related to the monoclonal antibody component of the medicine and, with the absence of reports describing an association, does not currently appear to be associated with ILD.

The New Zealand data sheets are largely consistent with international prescribing information. However, the pertuzumab data sheet does not list ILD as an ADR. This is included in the United Kingdom, Ireland, Australia and Canada prescribing information. Canada also lists ILD as a reported ADR in the obinutuzumab data sheet.

Given that a number of monoclonal antibodies are emerging as being implicated in ILD, company assessment of this risk could be considered in Periodic Benefit-Risk Evaluation Reports (PBRERs) for pertuzumab, daratumumab and obinutuzumab.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The companies should be asked to assess the risk of interstitial lung disease in Periodic Benefit-Risk Evaluation Reports (PBRERs) for pertuzumab, daratumumab and obinutuzumab
- Any data sheet updates should be requested, for example, listing interstitial lung disease in the pertuzumab data sheet
- Any other regulatory action is required.

6.0 ANNEXES

1. CARM report

7.0 REFERENCES

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