of patients. Anaemia, neutropenia, pneumonia and thrombocytopenia were the most common serious adverse effects (grade 3 or 4) and occurred in 5% or more of patients.

In total, 26 patients died during the trials. Apart from progressive disease, causes included pneumonia (5 patients), sepsis (2 patients), secondary malignancy (2 patients), cardiac arrest (1 patient) and hypovolaemic shock (1 patient).

Bleeding-related adverse events were common with ibrutinib and ranged from bruising and nosebleeds to blood in the urine, gastrointestinal bleeding and intracranial haemorrhage. Warfarin, fish oil and vitamin E should not be given concomitantly with ibrutinib.

Atrial fibrillation is a risk with ibrutinib, particularly during acute infections or in people with a history of atrial fibrillation or other cardiac risk factors. Regular cardiac monitoring is recommended. Alternatives to ibrutinib should be considered in patients who need oral anticoagulants.

Blood counts should be monitored every month as severe neutropenia, thrombocytopenia and anaemia can occur. Skin cancers have been reported with ibrutinib so regular skin examination is important.

Ibrutinib caused a transient increase in lymphocyte count at the beginning of treatment in 75% of patients with chronic lymphocytic leukaemia and 35% of patients with mantle cell lymphoma. Lymphocytosis often occurred at the same time as a reduction in lymph node and spleen size and is thought to be a pharmacodynamic effect unrelated to progressive disease. Leukostasis (clumping of white blood cells) was occasionally reported and may be related to an increase in circulating lymphocytes. It can cause local hypoxaemia and bleeding which can present as headache, blurred vision, transient ischaemia, cerebrovascular accident and dyspnoea. Patients should be monitored closely and ibrutinib may need to be interrupted if this occurs.

Pharmacology and drug interactions

Ibrutinib is rapidly absorbed after oral administration and metabolised in the liver by cytochrome P450 (CYP) 3A4. The half-life is 4–6 hours and metabolites are eliminated in the faeces (90%) and urine (10%).

Co-administration of moderate or strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, erythromycin or verapamil should be avoided. If they are needed, the ibrutinib dose should be reduced to 140 mg or interrupted for up to a week. Avoid grapefruit and Seville oranges as they can inhibit CYP3A4.

Strong CYP3A4 inducers and drugs that increase the pH of the stomach can decrease ibrutinib concentrations and are not recommended. St John's wort should also be avoided. As ibrutinib could theoretically inhibit intestinal P-glycoprotein, substrates of this transporter with a narrow therapeutic index (e.g. digoxin) should be taken at least six hours before or after the ibrutinib dose.

Conclusion

Ibrutinib offers another option for people with chronic lymphocytic leukaemia or mantle cell lymphoma, particularly those who have relapsed after previous treatments. Adverse effects are common and sometimes severe so patient monitoring is very important with this drug.

T T manufacturer provided additional useful information

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Pembrolizumab

Approved indication: metastatic melanoma
Keytruda (MSD)
vials containing 50 mg powder
Australian Medicines Handbook section 14.2.1

Along with vemurafenib[1], dabrafenib[2] and trametinib[3], pembrolizumab is approved for metastatic melanoma. Like ipilimumab[4], it is an immune checkpoint inhibitor that works by modulating the patient's own immune response to tumour cells.[5]

Pembrolizumab was formerly known as MK3475 and lambrolizumab. It is a humanised monoclonal antibody that blocks the interaction between programmed death 1 (PD-1) on T cells with its ligands PD-L1 and PD-L2 on immune and tumour cells. Blocking this interaction boosts the immune response and potentially leads to tumour regression.

This antibody is indicated as monotherapy for inoperable or metastatic melanoma. It is given intravenously (over 30 minutes) every three weeks. The drug's terminal half-life is approximately 26 days. The drug is catabolised and its clearance is not affected by mild–moderate renal impairment or mild hepatic impairment. Pembrolizumab has not been studied in patients with more severe renal or hepatic impairment.

Pembrolizumab has been assessed in a number of clinical trials. A phase I non-randomised trial enrolled 135 patients with advanced disease. The majority of participants (69%) had received previous systemic treatment, including chemotherapy, immunotherapy, or a BRAF inhibitor. Patients were given pembrolizumab 10 mg/kg every two or three weeks, or 2 mg/kg every three weeks. Across all doses, 38% of patients who could be evaluated had a confirmed response to treatment (see Table). The estimated median progression-free survival was over seven months and median overall survival was not reached.[6]

This phase I trial was expanded to include another cohort of patients who were refractory to ipilimumab and, if they had the BRAF mutation, had previously been treated with a BRAF or MEK inhibitor, or both. They were randomly assigned to pembrolizumab 2 mg/kg or 10 mg/kg every three weeks. Just over a quarter of patients responded to treatment and 58–63% were still alive after a year (see Table).[7] The efficacy of pembrolizumab in the phase I trial seemed to be independent of the dose.[6,7]

An analysis of 146 patients who received pembrolizumab 2 mg/kg found that response rates were better in those who had not previously been treated with ipilimumab compared with those who had (37% vs 26%). The median duration of progression-free survival was also longer (36 vs 22 weeks). At six months, overall survival was similar in ipilimumab-naïve and pre-treated patients (79% vs 83%). This analysis has not yet been published in full.

A randomised phase III trial compared pembrolizumab to ipilimumab. All enrolled patients had advanced melanoma but only 34% had been previously treated with systemic therapy. Pembrolizumab 10 mg/kg every two or three weeks improved progression-free and overall survival compared to ipilimumab. Response rates were also better with pembrolizumab (see Table).[8]

In the safety cohort of 411 patients, the most common treatment-related adverse events included arthralgia (14.8%), diarrhoea (14.8%), fatigue (30.2%), nausea (10%), pruritus (22.8%), cough (11.1%) and rash (19.8%). Albumin (36.7%), haemoglobin (51.6%) and lymphocytes (28.2%) went down with pembrolizumab. Decreased calcium (28.5%) and sodium (32.6%) concentrations were also observed. Liver function should be monitored as increases in alanine aminotransferase (23.6% of patients), alkaline

Table **Efficacy of pembrolizumab in metastatic melanoma**

Phase I trial[6]			
	Pembrolizumab 10 mg/kg every 2 weeks (52 patients)	**Pembrolizumab** 10 mg/kg every 3 weeks (45 patients)	**Pembrolizumab** 2 mg/kg every 3 weeks (20 patients)
Response rate‡	52%	27%	25%
Phase I trial – expanded cohort[7]			
	Pembrolizumab 10 mg/kg every 3 weeks (76 patients)	**Pembrolizumab** 2 mg/kg every 3 weeks (81 patients)	
Response rate‡	26% (1 complete and 19 partial responses)	26% (1 complete and 20 partial responses)	
Median progression-free survival	14 weeks	22 weeks	
Overall survival at 12 months	63%	58%	
Phase III trial[8]			
	Pembrolizumab 10 mg/kg every 2 weeks (279 patients)	**Pembrolizumab** 10 mg/kg every 3 weeks (277 patients)	**Ipilimumab** 3 mg/kg every 3 weeks (278 patients)
Response rate‡	33.7% (14 complete, 80 partial responses)	32.9% (17 complete, 74 partial responses)	11.9% (4 complete, 29 partial responses)
Median progression-free survival	5.5 months	4.1 months	2.8 months
Overall survival at 12 months	74.1%	68.4%	58.2%

‡ Complete and partial responses were based on assessment of target and non-target lesions according to the RECIST 1.1 criteria.[6]

phosphatase (22.6%) and aspartate aminotransferase (27.7%) were common.

Because of pembrolizumab's mechanism of action, immune-mediated adverse reactions are a concern. In the safety cohort, these included pneumonitis (12 patients), colitis (4 patients), hepatitis (2 patients) and nephritis (3 patients). Immune-mediated endocrinopathies have also been reported including hypophysitis (2 patients), type 1 diabetes, hyperthyroidism (5 patients) and hypothyroidism (34 patients). Monitoring blood glucose and thyroid function at the start and during pembrolizumab therapy is recommended. Depending on severity of these events, pembrolizumab should be interrupted or stopped and patients should be treated with corticosteroids. Severe infusion-related reactions have occasionally been reported with pembrolizumab and this is a contraindication to further treatment.

More patients discontinued the 10 mg/kg dose than the 2 mg/kg dose because of an adverse event.[7] The most common reasons for stopping pembrolizumab were pneumonitis, renal failure and pain.

Pembrolizumab is a category D drug in pregnancy. Although there are no data in pregnant women, blocking PD-1 in animals increases fetal loss. Contraception should be used during and for four months after treatment has finished.

The recommended dose of pembrolizumab is 2 mg/kg every three weeks. Around a quarter of patients with pre-treated metastatic melanoma responded to this dose. Response rates were better in those who had not previously been treated with ipilimumab. Autoimmune adverse reactions are a problem with this drug and regular patient monitoring is vital. Patients do not need to carry the BRAF mutation to be eligible for pembrolizumab.

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The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).