

PTAC meeting held on 5 & 6 November 2015

(minutes for web publishing)

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not a complete record of the PTAC meeting; only the relevant portion of the minute relating to PTAC's discussion about the application for pembrolizumab (Keytruda). This document will be updated in due course.

PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

1 Pembrolizumab for metastatic or unresectable melanoma stage III or IV

Application

- 1.1 The Committee considered an application from Merck Sharpe and Dohme (MSD) for the funding of pembrolizumab (Keytruda) for the treatment of patients with metastatic or unresectable melanoma stage III or IV.

Recommendation

- 1.2 The Committee **recommended** that pembrolizumab be funded for the treatment of metastatic or unresectable melanoma stage III or IV with low priority.
- 1.3 The Committee further **recommended** that it reconsider the funding application for ipilimumab (Yervoy, Bristol Myers Squibb (BMS), including review of recently published long term follow-up data.
- 1.4 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people in New Zealand; (iii) The availability and suitability of existing medicines; therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 1.5 The Committee noted that the application had been considered by its Cancer Treatments Subcommittee (CaTSoP) at its 18 September 2015 meeting. Members reviewed draft minutes from this meeting and noted CaTSoP's recommendation that pembrolizumab be funded for the treatment of metastatic or unresectable melanoma stage III or IV with low priority.
- 1.6 The Committee noted that New Zealand has a very high incidence of advanced melanoma and considered that there was an unmet health need for effective new treatments. The Committee noted that pembrolizumab was the first in a new class of monoclonal antibody programmed cell death (PD-1) inhibitors in development for treatment of a range of cancers. Members noted that other PD-1 inhibitors were also in late stage development, for example Bristol-Myers Squibb's nivolumab. Members noted that both nivolumab and pembrolizumab needed to be administered in hospital intravenously every 2 or 3 weeks depending on the dosing regimen used.
- 1.7 The Committee noted the supplier provided evidence in support of its application from two studies Keynote-001, a Phase I study and Keynote-006, a randomised Phase III study. Members also noted that PHARMAC staff provided additional evidence from a third study, Keynote-002, a randomised phase II study. Members noted that there were no studies comparing pembrolizumab directly with dacarbazine, the currently funded melanoma treatment in New Zealand.
- 1.8 The Committee reviewed evidence from Keynote-001 (Hamid et al. N Engl J Med. 2013;369:134-44; Robert et al. Lancet. 2014;384:1109-17) which was an open-label, multicentre, Phase I dose escalation study in patients with locally advanced or metastatic melanoma or non-small cell lung cancer. Members noted that this study

enrolled several cohorts with different dosing regimens (2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks and 10 mg/kg every 3 weeks) in both treatment naïve and pre-treated populations.

- 1.9 The Committee noted that results of the primary efficacy measure in Keynote-001 of overall response rate (ORR) varied across the dosing cohorts and patient populations examined. Robert et al. reported an ORR of 26 % in a pooled analysis of ipilimumab-refractory advanced melanoma patients treated with pembrolizumab at doses of 2 mg/kg or 10 mg/kg every 3 weeks. Unpublished evidence provided by the supplier reported an ORR of between 31 and 44% in ipilimumab-naïve patients across the dosing cohorts. Members noted that Hamid et al. reported an ORR of 52% in the pooled population of ipilimumab-naïve and pre-treated patients receiving the 10 mg/kg every 2 weeks regimen. Members noted that median progression free (PFS) survival ranged from 3.3 months for ipilimumab-refractory patients treated with pembrolizumab at 2 mg/kg every 3 weeks to 8.7 months for ipilimumab-naïve patients treated with pembrolizumab at 10 mg/kg every 2 weeks.
- 1.10 The Committee noted that pembrolizumab caused pruritus (itching) in approximately one quarter of all patients and fatigue in approximately one third of patients, and 3% of patients reported severe, grade 3, fatigue. Members noted that severe fatigue interferes with patient's quality of life and activities of daily living, with patients needing to rest for more than half of the day. Members considered that overall the toxicity profile of pembrolizumab appeared more favourable than ipilimumab, however, it was noted that given the short duration of the studies published to date, the long-term toxicity profile of pembrolizumab remains unknown.
- 1.11 The Committee considered that the 10mg/kg fortnightly dosing regimen appeared to produce numerically higher response rates, with minimal evidence for increased toxicity, compared with the other two dosing regimens examined (2 mg/kg three-weekly or 10 mg/kg three-weekly). The Committee reviewed evidence from Keynote-002 (Ribas et al. Lancet Oncol 2015;16:908–18.) which was a randomised phase II trial comparing two dosing regimens of pembrolizumab (2 mg/kg or 10 mg/kg) given every 3 weeks with investigator-choice chemotherapy in 540 patients with unresectable stage III or stage IV melanoma refractory to prior treatment with ipilimumab and, if BRAFV600 mutant-positive, refractory to previous treatment with a BRAF or MEK inhibitor or both. Members noted that investigator-choice chemotherapies comprised paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide.
- 1.12 The Committee noted that median PFS as assessed by central review (the primary endpoint of the study) was 2.9 months in both of the pembrolizumab groups compared with 2.7 months in the investigator-choice chemotherapy treatment group. However, because the first tumour assessment was conducted at 12 weeks and more than half of the patients in each treatment group had progressed at this time, members considered that these results were likely confounded by timing of the assessment.
- 1.13 The Committee noted that based on 410 progression-free survival events, progression-free survival was improved in patients assigned to pembrolizumab 2 mg/kg, HR 0.57, (95% CI 0.45–0.73), $p < 0.0001$, and pembrolizumab 10 mg/kg HR 0.50 (95% CI 0.39–0.64), $p < 0.0001$ compared with chemotherapy. 6-month progression-free survival was 34% (95% CI 27 to 41) in the pembrolizumab 2 mg/kg group, 38% (95% CI 31 to 45) in the 10 mg/kg group, and 16% (95% CI 10 to 22) in the chemotherapy group.

- 1.14 The Committee reviewed evidence from Keynote-006 (Robert et al. N Engl J Med. 2015;372:2521-32) which was a randomised, controlled, phase III study of pembrolizumab, given at 10 mg/kg every 2 weeks (n=279) or every 3 weeks (n=277). Treatment was given until either disease progression or the onset of unacceptable side effects, an investigator's decision to discontinue treatment, withdrawal of patient consent, or 24 months of therapy; and was compared with four doses of ipilimumab (at 3 mg/kg) in patients with unresectable stage III or IV melanoma who had received no more than one previous systemic therapy.
- 1.15 The Committee noted that median PFS, the primary endpoint of the study, was 5.5 months (pembrolizumab 10 mg/kg every 2 weeks), 4.1 months (pembrolizumab 10 mg/kg every 3 weeks), and 2.8 months (ipilimumab) respectively. Members noted that, based on 502 total progression-free survival events, hazard ratios for disease progression for pembrolizumab versus ipilimumab were 0.58 (95% CI 0.46 to 0.72), $P < 0.001$, for the two-weekly regimen and 0.58 (95% CI 0.47 to 0.72), $P < 0.001$, for the three-weekly regimen. Members further noted that median overall survival (OS) was not reached in any of the arms, but hazard ratios for death for the two pembrolizumab regimens were 0.63 (95% CI 0.47 to 0.83), $P < 0.0005$, and 0.69 (95% CI 0.52 to 0.90), $P = 0.0036$, compared to ipilimumab.
- 1.16 The Committee noted that response rates were 34% for pembrolizumab 10 mg / kg every 2 weeks arm ($P < 0.001$ compared to ipilimumab), 33% for pembrolizumab 10 mg / kg every 3 weeks arm ($P < 0.001$ compared to ipilimumab), and 12% for ipilimumab arm. Complete responses were seen in 5%, 6% and 1.4% of these patients respectively. Members noted that in the above 34%, 33% and 12% of patients who responded to treatment in each group, responses were ongoing in 89%, 97%, and 88% respectively at the time of the analysis (median follow-up of 7.9 months). Members considered that these results indicated that between 30 and 32% of all patients treated with pembrolizumab at 10 mg / kg experienced a durable response within the time-frame of follow up in the report, i.e. response ongoing at 7.9 months median follow-up, with between 1 and 4% experiencing only a short term response and the remaining two-thirds, between 66 and 67% of patients, having no response to pembrolizumab treatment. The Committee noted that grade 3 to 5 severe adverse events occurred in 13% and 10% of patients in the pembrolizumab groups compared with 20% in the ipilimumab group.
- 1.17 The Committee noted that there was some evidence to suggest that patients positive for PD-L1 expression may benefit most from pembrolizumab, which may be useful for targeting this treatment and improving its cost-effectiveness. However, members considered that the evidence for such targeting was currently weak.
- 1.18 The Committee considered that the evidence from Keynote-006 was of good strength and quality and indicates that, at least in the short term, pembrolizumab 10 mg / kg is likely more efficacious and less toxic than ipilimumab. However, the Committee considered that it was not possible to draw robust conclusions about the precise magnitude of benefit of pembrolizumab compared to dacarbazine by comparing the results from Keynote-006 with the ipilimumab Phase 3 study (Hodi et al. N Engl J Med. 2010;363:711-23), because the patient populations in these two studies were different. Members noted that 5 year survival data have recently been published from a randomised phase III study comparing a higher dose of ipilimumab (10mg / kg) plus dacarbazine with placebo plus dacarbazine in patients with previously untreated, unresectable Stage III or IV melanoma (Maio et al. J Clin Oncol 2015;33:1191-96). Members recommended that the Committee review these data more formally in the context of reconsidering the funding application for ipilimumab (Yervoy, Bristol Myers Squibb).

- 1.19 The Committee noted ongoing studies examining combinations of PD-1 inhibitors, ipilimumab and BRAF/MEK inhibitor treatments, all being high cost treatments on their own.
- 1.20 The Committee considered the evidence for pembrolizumab in advanced melanoma was still developing. Given the short duration and limitations of the reported evidence, members considered that whilst the treatment was an advance, there remained uncertainty regarding the optimal dosing regimen and both the long-term benefits and risks of pembrolizumab treatment. Members also considered that the pricing being sought by the supplier for pembrolizumab was excessively high, adversely affecting its cost-effectiveness.

