Cancer Treatments Subcommittee of PTAC
Meeting held 18 September 2015

(minutes for web publishing)

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

The Cancer Treatment Subcommittee 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.

A draft version of this Subcommittee minute was reviewed by PTAC at its meeting 5 & 6 November 2015 and the final version will be reviewed by PTAC at its meeting 11 &12 February 2016.

1 Pembrolizumab for metastatic melanoma

Application

1.1 The Subcommittee 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 Subcommittee **recommended** that pembrolizumab should be funded for the treatment of metastatic or unresectable melanoma stage III or IV with low priority. The Subcommittee noted that its low priority rating was influenced by the early evidence base, and consequent uncertainty about pembrolizumab's longer term benefits and potential risks, as well as its very high cost.

1.3 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

1.4 The Subcommittee considered that New Zealand had a very high incidence of advanced melanoma and considered that there was an unmet health need for new treatments. The Subcommittee noted that three other treatments for melanoma had been considered by it and/or PTAC in recent years, namely, ipilimumab (Yervoy) for previously treated unresectable (stage IIIC or stage IV) melanoma and vemurafenib (Zelboraf) and dabrafenib (Tafinlar) for BRAF V600 mutation positive unresectable (stage IIIC or stage IV) melanoma. Members noted that to date PTAC had recommended all be declined primarily due to their very poor cost effectiveness at the proposed prices. Members also noted a number of other new treatments were in development for the treatment of advanced melanoma which would likely be submitted to PHARMAC in coming months.

1.5 The Subcommittee 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 PD-1 down-regulates the immune system, therefore PD-1 inhibitors work by activating the patient's own immune system to attack the cancer cells. Members noted that as well as MSD's pembrolizumab, Bristol-Myers Squibb recently had its PD-1 inhibitor (nivolumab) approved by regulators overseas for the treatment of advanced melanoma. Members noted that both nivolumab and pembrolizumab were administered intravenously.

1.6 The Subcommittee noted that the evidence base *for pembrolizumab in melanoma comprised 3 studies; a phase I/II study Keynote-001, a randomised phase II study Keynote-002 and a randomised phase III study Keynote-006.* Members noted that t*here are no studies comparing pembrolizumab with dacarbazine, the currently funded melanoma treatment in New Zealand. Members noted that Keynote-001 had only been partly published and that Keynote-002 was not included in the supplier's submission.*

1.7 The Subcommittee noted that Keynote-001 (which has been part published in Hamid, O et al Engl J Med 2013; 369:134-144 and Robert, C et al. Lancet. 2014; 384: 1109–1117) was an open-label, multicentre, Phase I study in patients with locally advanced or metastatic melanoma or non-small cell lung cancer. Members noted that this was a complex study which was initially designed as a dose escalation study and was then amended to enrol several cohorts of patients examining various dosing regimens including 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks and 10 mg/kg every 3 weeks in various populations. Members noted that published data was limited to ipilimumab-refractory melanoma patients and a cohort of treatment naïve patients, however, the supplier also provided unpublished evidence from all of the ipilimumab treatment naïve patients enrolled in this study. Members noted that various cohort and pooled analyses of patients from different cohorts were undertaken.

1.8 The Subcommittee 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, with ORR of 26% reported by Robert et al 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 compared with the unpublished evidence provided by the supplier of 31-44% ORR in ipilimumab naïve patients across the dosing cohorts. The Subcommittee noted that the 10 mg/kg Q2W dosing regimen appeared to produce numerically higher response rates as compared to the other two dosing regimens examined (2 mg/kg Q3W or 10 mg/kg Q3W). Members noted that median progression free (PFS) survival ranged from 3.3 months for ipilimumab refractory patients treated pembrolizumab at 2 mg/kg Q3W to 8.7 months for ipilimumab naive patients treated pembrolizumab at 10 mg/kg Q2W.

1.9 The Subcommittee noted that pembrolizumab treatment was associated with fatigue, pruritus, and rash as well as a number of immune mediated side effects. Members noted that whilst the majority of adverse events were grade 1 or 2 around 3% of patients reported grade 3 fatigue which would impact on patients activities of daily living.

1.10 The Subcommittee noted that Keynote-002 (Ribas, A et al. Lancet Oncol August 2015; 16: 908–18.) was a randomised phase 2 trial of patients with unresectable stage III or stage IV melanoma with ECOG performance status 0-1 and confirmed progressive disease within 24 weeks after two or more ipilimumab doses and, if BRAFV600 mutant-positive, previous treatment with a BRAF or MEK inhibitor or both. Members noted that this study was not provided by the supplier but considered this was a reasonable omission given the funding application was primarily for funding of pembrolizumab for ipilimumab treatment naïve patients. Members noted that in this study 540 patients were randomly assigned (1:1:1) to pembrolizumab 2 mg/kg (n=180) or pembrolizumab 10 mg/kg (n=181) given intravenously every 3 weeks or investigator-choice chemotherapy (n=179) (paclitaxel plus carboplatin, paclitaxel, carboplatin [eliminated with protocol amendment one], dacarbazine, or oral temozolomide). Members noted that 86 (48%) of patients randomised to chemotherapy crossed over to pembrolizumab treatment, with 46 randomly assigned to receive 2 mg/kg and 40 to receive 10 mg/kg.

1.11 The Subcommittee noted that the primary endpoint was progression-free survival by independent central review, with secondary endpoints including objective response rate, complete or partial response rates by central review, response duration, the time from best overall response of complete or partial response until disease progression; and safety. Members noted that the median PFS as assessed by central review was 2.9 months in both of the pembrolizumab groups compared with 2.7 months in the chemotherapy treatment group. Members noted that

pembrolizumab did show significant improvement in PFS, with hazard ratios of 0.57 (95% CI 0.45–0.73) for pembrolizumab 2 mg/kg and 0.50 (95% CI 0.39–0.64) for 10 mg/kg compared with chemotherapy (p<0.0001 for both). Members further noted that pembrolizumab significantly improved PFS when assessed by investigator review and agreed with the author's view that possible investigator bias in this partly open-label trial might explain the greater effect size as compared with central review results. Overall, members considered that the median progression free survival results from this study were unreliable.

1.12 The Subcommittee noted that Keynote-006 (Robert, C et al. N Engl J Med. 2015 Jun 25;372(26):2521-32) was a randomized, controlled, phase III study that enrolled patients with unresectable stage III or IV melanoma with ECOG performance status 0-1 who had received no more than one previous systemic therapy for advanced disease (approximately 65% of patients were treatment naïve). Members noted that 834 patients were randomised in a 1:1:1 ratio to receive pembrolizumab 10 mg/kg every 2 weeks (n=279) or every 3 weeks (n=277) or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks (n=278) with pembrolizumab administered intravenously over a 30-minute period and continued until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, withdrawal of patient consent, or 24 months of therapy. Members noted that the pembrolizumab doses used in this study were higher than the 2 mg/kg Q3W dosing recommended on the Medsafe approved datasheet and being sought by the supplier for funding.

1.13 The Subcommittee noted that median progression free survival (PFS) the primary endpoint of the study, was 5.5 months (pembrolizumab 10 mg/kg Q2W), 4.1 months (pembrolizumab 10 mg/kg Q3W) and 2.8 months (ipilimumab) with hazard ratios for disease progression for pembrolizumab versus ipilimumab of 0.58 (95% CI, 0.46 to 0.72; P<0.001) for the 2-week regimen and 0.58 (95% CI, 0.47 to 0.72; P<0.001) for the 3-week regimen. Median overall survival (OS) was not reached in any of the arms, but 1 year survival rates were 74.1% ,68.4% and 58.2 % respectively, with hazard ratios for death for the two pembrolizumab regimens of 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) versus ipilimumab. Members 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.

1.14 The Subcommittee noted that the efficacy results reported for the ipilimumab arm of Keynote-006 were somewhat better than reported in the ipilimumab Phase 3 study (Hodi et al N Engl J Med 2010; 363:711-23), but considered that this may be due to Keynote-006 including pre-treated and treatment naïve patients, whereas in Hodi et al all patents were pre-treated.

1.15 The Subcommittee considered that overall there was good evidence that pembrolizumab had some efficacy; however, members considered it was a very difficult application to consider as the clinical trials presented and analyses undertaken all had limitations. Members considered that at this time there was only weak evidence to inform an estimate of the magnitude and duration of benefit of pembrolizumab compared with currently funded treatment. Members considered that the evidence was complex and rapidly evolving and that longer term evidence was needed to be more certain of the benefits and harms of this new class of treatment. Members noted that whilst the current adverse event profile of pembrolizumab appeared manageable the potential for longer term immune-mediated toxicities needed to be considered. Members expressed some doubt about the supplier's conclusions regarding dose equivalence across the range of doses examined in the

various clinical trials, with some members considering that there may be a dose effect favouring higher and more frequent dosing regimens.

1.16 The Subcommittee considered that there was a significant discrepancy in the consumer and media-reported view of the benefit of pembrolizumab and the available evidence. Members considered that whilst there was a high unmet need for new treatment options for melanoma patients the pricing being sought was excessive given the current early, and evolving, nature of the evidence and lack of certainty for its longer term benefit and potential risks. [redacted]

1.17 The Subcommittee noted that the application for pembrolizumab would likely be reviewed by PTAC at its November 2015 meeting.