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Technology Assessment Report No. 271

Preliminary Economic Analysis on pembrolizumab for metastatic or unresectable melanoma stage III or IV

December 2015

Summary of Proposal

Pharmaceutical Pembrolizumab (Keytruda®) 50mg lyophilised powder for reconstitution per vial
Supplier Merck Sharpe and Dohme (MSD)
Proposed Indication Monotherapy for the treatment of unresectable or metastatic stage III or IV melanoma.
Dosing 2mg/kg by infusion every three weeks until disease progression or unacceptable toxicity
Pharmaceutical Price [redacted] per 50mg vial, before proposed confidential rebate and annual net expenditure caps
Current Treatment Dacarbazine

Executive Summary

Proposal under Assessment

Pembrolizumab (Keytruda) as monotherapy for the treatment of unresectable or metastatic melanoma (Stage III or IV).

Objectives

The objective of this assessment is to assess the cost-effectiveness of pembrolizumab compared with dacarbazine as monotherapy for the treatment of unresectable or metastatic melanoma (Stage III or IV). This is a preliminary assessment as defined in version 2.2 of the Prescription for Pharmacoeconomic Analysis (PFPA).

Clinical Effectiveness Review

The main evidence used for this economic assessment is from the KEYNOTE-006 Phase III randomised controlled trial, as reported by Robert, Schachter *et al* (2015). Most of the results presented in the Robert et al. publication are from the first interim analysis, except for overall survival results, which are from the second interim analysis.

Cost-Utility Analysis

A decision-analytic Markov model was constructed to simulate the different treatment strategies. The analysis was based on the methods described in version 2 of the Prescription for Pharmacoeconomic Analysis (PFPA), and was developed using clinical advice from the Pharmacology and Therapeutic Advisory Committee (PTAC) and its Cancer Treatments Subcommittee (CaTSoP).

Key inputs in the model include overall survival and progression-free survival derived from KEYNOTE-006 (Robert, Schachter *et al*, 2015) and an indirect comparison to dacarbazine using evidence derived from the trial reported in Robert, Thomas *et al* (2011). Costs are estimated from the perspective of the funder and include pharmaceutical, pharmaceutical administration, pharmaceutical distribution and medical management costs. Quality of life scores are based on the NZEQ-5D. Costs and benefits are discounted at PHARMAC's discount rate for cost-utility analysis of 3.5%.

The base case of this analysis assumes that annual net costs exceed the supplier's proposed confidential net expenditure cap, thereby in effect reducing the average net pharmaceutical cost per vial and patient treatment cycle, and that DHB hospitals have sufficient infusion service capacity to treat all patients who would be eligible to receive funded pembrolizumab. Sensitivity analyses consider higher and lower patient uptake numbers, as well as effect size, health sector costs and quality of life.

The cost effectiveness of pembrolizumab compared with dacarbazine for the treatment of unresectable or metastatic melanoma is estimated to be in the range of [redacted] The results of this cost utility analysis (CUA) are sensitive to the treatment effect size, the utility of progressed disease and cost of treatment. The uncertainty in the treatment effect size is mostly due to the current uncertainty about the magnitude and long-term durability of any benefit. Uncertainty in cost is particularly sensitive to the assumed number of patients accessing treatment.

Budget Impact Analysis

PHARMAC staff note that the New Zealand Cancer Registry records the numbers of patients with newly diagnosed melanoma and number of deaths attributed to melanoma up until 2012. However,

due to the registry not capturing information on the progression of melanoma from one stage to another, we have used mortality figures as a surrogate for the likely number of patients with stage III and IV disease and thus eligible to commence treatment with pembrolizumab each year (ie, we have made the assumption that all those who die of melanoma would have late stage disease). PHARMAC staff estimate this figure to be approximately 380 patients in 2016.For this analysis, we have used the supplier's proposed confidential rebate structure. The incremental cost-utility estimate applies at the date of any such listing; the budget impact numbers would have to be deferred appropriately. We have assumed that there would be a backlog of an additional 20% of estimated first year patients that would commence treatment in year 1, made up of patients already accessing pembrolizumab prior to the date of listing either through private funding or compassionate access/clinical trials. We have also assumed that 60% of newly diagnosed patients who commence funded treatment with pembrolizumab would remain on treatment until disease progression or unacceptable toxicity. This figure is based on data from the KEYNOTE-006 trial and includes those people who respond to treatment, either completely or partially, and those whose disease is stable whilst on pembrolizumab treatment. The median duration of treatment until disease progression for patients with responsive disease in KEYNOTE-006 was 28 three-weekly cycles and therefore we have assumed that for these patients the median time on treatment would be 20 months. This analysis also assumes that the reminder of patients (40%) who do not respond to treatment or have stable disease would cease treatment after 4 cycles, as under the supplier's proposed Special Authority access criteria these patients would not be eligible for an additional 4 cycles (3 months) ongoing funded pembrolizumab treatment.

There is significant uncertainty about the rate at which new eligible patients would commence pembrolizumab treatment. This is because there is uncertainty around both uptake and duration of treatment for existing patients. There is also uncertainty about how quickly DHB hospitals could expand specialist appointments, infusion service capacity and related services needed to administer pembrolizumab for the potential number of additional patients estimated to be potentially eligible for funding.

We estimate that the net DHB budget impact of funding pembrolizumab on the Pharmaceutical Schedule for patients with unresectable or metastatic melanoma stage III or IV to be approximately [redacted] in the first full year, growing to approximately [redacted] in the fifth year. This includes associated non-pharmaceutical costs to the DHB hospital budget such as compounding, scans, infusion service costs, and specialist's and nurse's time.

1 Context

1.1 Proposal Under Assessment

Pharmaceutical Pembrolizumab (Keytruda®) 50mg lyophilised powder for reconstitution per vial
Supplier Merck Sharpe and Dohme (MSD)
Proposed Indication Monotherapy for the treatment of unresectable or metastatic stage III or IV melanoma.
Dosing 2mg/kg by infusion every three weeks until disease progression or unacceptable toxicity
Pharmaceutical Price [redacted] per 50mg vial, before proposed confidential rebate and net expenditure cap
Current Treatment Dacarbazine

An application for the funding of pembrolizumab for the treatment of unresectable or metastatic melanoma stage III and IV was received from MSD in May 2015. The application included an economic analysis, which has been reviewed by PHARMAC staff (see section 3.2).

The application was reviewed by the PTAC in November 2015, and by its Cancer Treatments Subcommittee (CaTSoP) in September 2015. The full relevant minutes from these meetings are included in Section 1.2 below.

The results of this economic analysis may be considered as part of PHARMAC's application of the Decision Criteria ('criterion 5') when considering the funding application for pembrolizumab for patients with unresectable or metastatic melanoma stage III or IV – where cost-effectiveness is currently one of PHARMAC's nine Decision Criteria.

1.2 PTAC and Subcommittee minutes

1.2.1 Relevant PTAC minute, November 2015

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-naive 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 31to 45) in the 10 mg/kg group, and 16% (95% CI 10to 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 [redacted]

1.2.2 Relevant CaTSoP minute, September 2015

5 Pembrolizumab for metastatic melanoma

Application

5.1 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

5.2 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.

5.3 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

5.4 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 (Ze boraf) 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.

5.5 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.

5.6 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 there 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.

5.7 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.

5.8 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.

5.9 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.

5.10 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.

5.11 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.

5.12 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.

5.13 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.

5.14 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.

5.15 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.

5.16 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. Members noted that the public pricing being sought by MSD was higher than it is currently receiving for pembrolizumab through its private cost share programme.

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

1.3 Description of Condition and Patient Population

Melanoma is a malignant tumour of melanocytes; the cells that produce dark skin pigmentation. Melanomas predominantly occur in skin, but can be found in other parts of the body, including the bowel and the eye. Melanoma is less common than other skin cancers such as squamous and basal cell carcinomas, however, it is the most aggressive.

New Zealand has the highest melanoma incidence rate in the world. Melanoma is the fourth most common cancer in NZ. In 2008, 2,256 people were diagnosed with melanoma and there were a total of 317 deaths from melanoma (202 in men, 115 in women). The majority of melanoma cases, around 70%, occur in people aged 50 years and older. Melanoma rates in NZ are increasing; between 1998 and 2008 the rates of melanoma diagnosis increased by 12 and 16 percent for males and females, respectively. The age standardised incidence rate of melanoma is approximately 7 times higher in non-Māori compared with Māori, however, Māori have a significantly higher risk of being diagnosed with more advanced and aggressive disease compared with non-Māori.

The New Zealand Cancer Registry records the numbers of newly diagnosed melanoma and number of deaths attributed to melanoma up until 2012. However, the registry does not capture information on the progression of melanoma from one stage to another. This analysis uses the recorded mortality figures as a surrogate for the potential number of patients with unresectable or metastatic melanoma stage III or IV that may be eligible for funded treatment with pembrolizumab each year (ie, we have made the assumption that all of those who die of melanoma have unresectable/metastatic stage III and IV disease). PHARMAC staff estimates this figure to be approximately 380 patients in 2016, and based on the current trend in Cancer Registry recorded melanoma deaths we have assumed growth of approximately 10 patients each year.[i]

1.4 Melanoma prognosis and current treatment options

Early diagnosis and treatment is the key to minimising morbidity and mortality in patients with melanoma. The majority of patients with localised disease can be cured with surgical resection, however, some patients present with, or subsequently develop, advanced disease.

The prognosis for patients with advanced/metastatic (stage IV) melanoma is poor, the majority of patients will die within a year of diagnosis without treatment, with 5 year overall survival rates around 15-20% and 10-year survival about 10-15%. Cases of spontaneous remission have been reported in the literature, with reported incidence of complete spontaneous remission of primary melanoma, including metastatic melanoma with an occult primary lesion, ranging from 3.7% to 15%. Complete spontaneous remission of melanoma metastases is less frequent at about 0.23%, corresponding to around one in 400 patients (Kalialis, Drzewiecki *et al*). The precise mechanism of spontaneous remission remains unknown, it is thought that some event triggers the immune system to produce a stronger than normal response that results in regression of the melanoma cells. This stimulus may be an infection, surgical trauma or any other event that makes the melanoma cells unable to evade the immune response that follows.

Currently funded treatment options for advanced/metastatic melanoma in New Zealand include palliative radiation and/or surgery, immunotherapy, or chemotherapy treatment. Dacarbazine (also known as DTIC) is the main chemotherapy treatment currently used in New Zealand; however, its

[i] The growth in numbers of deaths from malignant melanoma is likely a period effect, due to a combination of an age effect (population ageing) and a cohort effect (increasing incidence of melanomas in cohorts of people exposed to excess sunburn events etc in previous decades, now maturing). Our assumptions regarding patient numbers differ from the assumptions provided in the Supplier's modelling, which appears to have assumed a static prevalent numbers of deaths; by contrast, in our analysis we note death counts for malignant melanoma for the years 2007 to 2011 have risen by 2% per year (faster than the average for the years 1998-2008), which is consistent with international narratives around the increasing burden of malignant melanoma from aging effects.

efficacy is limited. A pooled analysis of 23 randomised controlled trials indicated that the objective response rate (ORR) for 1,390 patients receiving dacarbazine alone was 15.3%, with the majority of these responses being partial (11.2% partial responses [PR], 4.2 % complete responses [CR]) (Lui, Cashin *et al*, 2007).

Where patients do respond to dacarbazine, responses are usually partial and of short duration, with median response duration of four to six months. Long-term follow-up of patients treated with dacarbazine indicates that overall only 1-2% of patients survive to six years, however, in the small number of patients that achieve a complete response to dacarbazine long term survival rates are 31% at 6 years (Hill, Krementz *et al*, 1984). Since dacarbazine monotherapy has not been investigated in a placebo-controlled trial, there is insufficient evidence to suggest an overall survival benefit with dacarbazine. Dacarbazine is generally well tolerated, with the major side effect being nausea and vomiting. Bone marrow suppression is usually modest, and alopecia and fatigue are minimal, allowing most patients to maintain relatively normal function while receiving therapy.

Immunotherapy with interferon alfa (or interleukin (IL)-2) has activity in some patients with metastatic melanoma but is not routinely used because of its poor tolerability.

There is an unmet health need in New Zealand for more effective funded treatments for patients with advanced melanoma.

1.5 New treatments

There are a range of new targeted and immune modulating treatments that have recently become available, or are in development, for advanced melanoma. PTAC and CaTSoP have considered funding applications for five of these medicines in recent years; pembrolizumab (Keytruda, MSD) vemurafenib (Zelboraf, Roche), ipilimumab (Yervoy, BMS), dabrafenib (Tafinlar, GSK/Novartis) and trametinib (Mekinist, Novartis).

Vemurafenib and dabrafenib are oral small molecules that target mutations on the BRAF gene that regulates cell growth, such mutations are present in approximately 40% of melanoma patients. Ipilimumab is a monoclonal antibody, administered intravenously, that targets CTLA-4, a protein receptor that down-regulates the immune system, thus by blocking CTLA-4 ipilimumab activates the patient's own immune system to attack melanoma cells.

The currently available data for these new treatments suggest there is some clinical benefit over currently funded dacarbazine treatment; however, given the lack of adequate control arms in many of the studies, or early cross-over where control arms are used, the magnitude of this benefit has some uncertainty.

GSK has recently gained approval for trametinib (Mekinist) an oral small molecule inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and kinase activity. Trametinib is given in combination with dabrafenib MEKINIST in combination with dabrafenib is indicated for the treatment of patients with BRAFV600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma or as monotherapy in patients who are intolerant to BRAF inhibitors or where BRAF inhibitors cannot be used. GSK submitted an application for trametinib and dabrafenib but then withdrew the application and resubmitted it as a dabrafenib application only. GSK subsequently divested its oncology portfolio to Novartis. Trametinib was recently approved by Medsafe and PHARMAC recently received an application for funding of dabrafenib combined with trametinib; this was considered by PTAC at its November 2015 meeting.

To date PTAC has recommended that vemurafenib, ipilimumab and dabrafenib all be declined, primarily due to uncertainty of magnitude of benefit and their very poor cost effectiveness at the proposed prices.

As at 1 November 2015, ipilimumab, dabrafenib and trametinib are funded on the PBS in Australia, vemurafenib is not.

1.6 Other New treatments

1.6.1 Programmed cell death (PD-1) inhibitors

Two PD-1 inhibitors have been approved overseas for use in advanced melanoma; nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, MSD). Like CTLA-4, PD-1 down-regulates the immune system, PD-1 inhibitors like nivolumab and pembrolizumab block PD-1 thus activating the patient's own immune system to attack melanoma cells. Both nivolumab and pembrolizumab are monoclonal antibodies administered intravenously.

Through their mechanism of action nivolumab and pembrolizumab have potential as treatments for a broad range of cancers. Nivolumab and pembrolizumab are both also approved overseas for the treatment of advanced non-small cell lung cancer (NSCLC), and both BMS and MSD are actively engaged in a range of studies in over 30 different cancer types including breast, head and neck, lung, renal, gastric and Hodgkin's Disease. We anticipate receiving a funding application for nivolumab for melanoma within the next quarter. BMS is currently conducting studies combining nivolumab with ipilimumab and we understand that MSD has partnered with several companies to conduct studies of pembrolizumab combined with various other novel, and existing, treatments.

1.7 Pharmaceutical Under Assessment

Based on preliminary Phase I data, pembrolizumab was granted accelerated (conditional) approval by the FDA in September 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (i.e. second line treatment) at a dose of 2 mg/kg every 3 weeks.

The FDA designated pembrolizumab a 'breakthrough' therapy. The FDA's criteria for 'breakthrough' are "a medicine that treats a serious or life-threatening condition and preliminary clinical evidence indicates that the medicine may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies". In October 2015 the FDA approved use of pembrolizumab for the treatment of advanced NSCLC and in August 2015 BMS submitted an application for first line treatment of unresectable or metastatic melanoma.

Pembrolizumab was approved in Australia by the TGA in April 2015 for both first and second line treatment of patients with unresectable or metastatic melanoma. Australia was the first country in the world to have first-line approved. The TGA approved the dose of 2 mg/kg every 3 weeks dosing of pembrolizumab.

Pembrolizumab was approved by the EMA in July 2015 for first and second line treatment of patients with unresectable or metastatic melanoma at a dose of 2 mg/kg every three weeks.

1.7.1 Medsafe review

MSD submitted an application for registration of pembrolizumab in New Zealand to Medsafe in April 2015 through the abbreviated route following the TGA approval. Medsafe granted MSD approval on 3 September 2015 to market pembrolizumab in New Zealand as monotherapy for the treatment of unresectable or metastatic melanoma in adults. The Medsafe datasheet details the recommended dosing to be 2 mg/kg administered intravenously over 30 minutes every 3 weeks; and that patients should be treated with pembrolizumab until disease progression or unacceptable toxicity.

Prior to Medsafe approval some NZ patients had been treated with pembrolizumab within the context of clinical trials, or MSD's early access programme for patients who had failed ipilimumab treatment with treatment duration limited to maximum of 24 months, however, as ipilimumab is not funded in NZ, we undetstand that few NZ patients have accessed pembrolizumab through this route.

Following approval of pembrolizumab by MedSafe, MSD launched a cost share programme (CSP) for private use of pembrolizumab in New Zealand. Patients enrolled in the programme pay [redacted] per 50mg vial of pembrolizumab, and receive some free cycles of treatment from MSD.

1.7.2 Supplier's application

The supplier has applied for funding of pembrolizumab subject to the following proposed Special Authority criteria:

> **Initial Application** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for maximum of 4 treatment cycles:
>
> 1. The patient has metastatic or unresectable melanoma stage III or IV
>
> **Renewal** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months where radiological assessment (preferably including CT scan) indicates melanoma has not progressed.
>
> Note: Some patients may experience pseudo-progression which can be a sign of response, if this is suspected further investigation may be required to determine response or progression.

This TAR analyses pembrolizumab for the proposed Special Authority. PHARMAC staff note that the supplier's proposed criteria would not limit funding to ipilimumab treatment-naïve patients, nor do they specify the dosing regimen or a maximum duration of treatment that would be funded. This is important, as the supplier's economic modelling assumes patients receiving funding would all be treatment-naïve and dosed at 2mg/kg once every 3 weeks. As discussed in section 4.1.2, PHARMAC assumes that all New Zealand patients are ipilimumab naïve as it is not funded.

The supplier also proposes a scenario where treatment is discontinued either at disease progression or after a maximum of 2 years; the latter is inconsistent with the Medsafe datasheet dosage recommendations. The TAR does not analyse this scenario.

2 Effectiveness Review

2.1 Literature Search Strategy

An opportunistic literature search for randomised controlled trials, review articles, meta-analyses, guidelines and economic analyses of pembrolizumab for melanoma was conducted by PHARMAC staff on 17 November 2015. Further searches were done to find trials comparing ipilimumab to dacarbazine.

The following websites were also searched:

- National Institute for Health and Care Excellence (UK): http://www.nice.org.uk/
- Canadian Agency for Drugs and Technology in Health: http://www.cadth.ca/
- Scottish Medicines Consortium: http://www.scottishmedicines.org.uk/
- Australian Pharmaceutical Benefits Scheme:
- http://www.health.gov.au/internet/wcms/publishing.nsf/Content/public-summary-documents
- Medsafe datasheets: http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp

The literature search undertaken by PHARMAC staff was supplemented by material provided by the supplier in its funding application.

Independent expert clinical advice was provided by the Pharmacology and Therapeutic Advisory Committee and its Cancer Treatments Subcommittee at their meetings held on 5 and 6 November 2015 and 18 September 2015 respectively.

2.2 Summary of evidence reviewed

The evidence base for pembrolizumab use in unresectable/metastatic melanoma comprises 3 studies; One phase I study, KEYNOTE-001, a randomised phase II study, KEYNOTE-002, and one randomised phase III study, KEYNOTE-006. Evidence from various time-points of these studies have been presented on numerous occasions at various cancer conferences in abstract and presentation form and the supplier has also provided some unpublished data in its application. There are no studies comparing pembrolizumab with the currently funded treatment for melanoma in New Zealand, dacarbazine, in treatment naïve patients with unresectable/metastatic melanoma. KEYNOTE-001 has only been partly published and KEYNOTE-002 enrolled patients who had been pre-treated with ipilimumab and if BRAF V600 mutant-positive, previous treatment with a BRAF or MEK inhibitor or both. A summary of the evidence available from these studies is provided below.

KEYNOTE-001: Part published in Hamid, Robert *et al* (2013) and Robert, Ribas *et al* (2014).

KEYNOTE-001 was an open-label, multicentre, Phase I study in patients with locally advanced or metastatic melanoma or NSCLC, it used of various pembrolizumab dosing regimens including 2 mg/kg every 3 weeks, 10 mg /kg every 2 weeks and 10 mg/kg every 3 weeks, treatment was administered until disease progression, intolerable toxicity, or consent withdrawal. Through a series of amendments the study evolved into four Phase II-like melanoma sub-studies, known as Parts B1, B2, B3 and D.

The primary endpoint of the study was overall response rate (ORR) and safety; the secondary endpoints include progression-free survival (PFS), overall survival (OS) and duration of response.

The trial was initially designed as a dose escalation study in patients with advanced malignancy, and was the first in-human study for pembrolizumab. This part of the study is now called Part A. As several patients in this study with melanoma had an objective response to treatment, the study was expanded to evaluate efficacy in melanoma in Part B (now Part B1 of the study). Part B1 was non-randomised and enrolled both ipilimumab treated and ipilimumab naïve patients, 57 patients received

10 mg/kg every 2 weeks, 56 received 10 mg/kg every 3 weeks and 22 received 2 mg/kg every 3 weeks.

Part B2 enrolled ipilimumab refractory patients while part B3 enrolled both ipilimumab treated and ipilimumab naïve patients, where patients were randomised to treatment with either 10 mg/kg every 2 (n=123) or 3 weeks (n=125). Part D was conducted in patients who were naïve to ipilimumab treatment, randomising patients to treatment with either 2 mg/kg every 3 weeks (n=51) or 10 mg/kg every 3 weeks (n=52).

[redacted]

KEYNOTE-001 – Part B Ipilimumab naïve and Ipilimumab-refractory patients (reported by Hamid, Robert et al (2013)

This publication reported outcomes from 135 patients treated with pembrolizumab. The initial cohort of patients who were enrolled received pembrolizumab[ii] as a 30-minute intravenous infusion, every 2 weeks at a dose of 10 mg/kg; patients enrolled in additional cohorts in Part B received pembrolizumab every 3 weeks at 2 mg/kg or 10 mg/kg in sequential or concurrent cohorts without randomisation. Treatment was continued until disease progression was confirmed, unacceptable toxic effects developed, or consent was withdrawn. The primary objective of this study was to evaluate the safety profile of pembrolizumab, and the secondary end point was a preliminary analysis of the antitumor activity of pembrolizumab, both in patients who had received prior treatment with ipilimumab and in those who had not.

Data from 135 patients with melanoma who were enrolled and treated according to protocol amendments 02, 03, and 04 were used for the analysis of adverse events. Of the 135 patients, 117 had radiographically measurable disease were included in the efficacy analysis of responses according to central review. All other efficacy analyses (an analysis of response on the basis of assessment by the investigator, progression- free survival, and overall survival) were based on data from all 135 patients. 48 patients had received prior treatment with ipilimumab and 87 had not.

Of the 135 patients who received at least one dose of pembrolizumab,[ii], 79% reported drug-related adverse events of any grade, and 13% reported grade 3 or 4 drug-related adverse events. Generalised symptoms, including fatigue and asthenia, fever and chills, myalgias, and headaches, were reported frequently but were of low grade in more than 95% of the cases. Rashes and pruritus were reported in 21% of the patients; grade 3 or 4 pruritus was reported in 1% of the patients, and grade 3 or 4 rash in 2%. Diarrhoea was reported in 20% of patients, with a single case of grade 3 treatment-related diarrhoea reported. Treatment-related pneumonitis was reported in 4% of the patients, Grade 3 or 4 elevations of aminotransferase levels were reported in 1% of the patients. Two

[ii] Pembrolizumab was formerly named lambrolizumab (MK-3475) and this is the drug name used in this paper

cases of grade 3 renal failure were reported. Both cases were potentially immune-mediated, and the patients' renal function improved with glucocorticoid therapy along with the discontinuation of pembrolizumab. Hypothyroidism was reported in 8% of the patients and was effectively managed with thyroid-replacement therapy.

The overall response rate during receipt of therapy, across all doses, on the basis of assessment by the investigator according to immune-related response criteria was 37%. The confirmed response rate across all doses, as assessed by central review according to RECIST, was 38% (44 of 117 patients). The median progression-free survival among the 135 patients, as estimated with the use of a Kaplan–Meier analysis, was more than 7 months. The estimated median overall survival had not been reached.

KEYNOTE-001 – Ipilimumab-refractory patients (published in Robert, Ribas et al (2014))

This publication report outcomes from 173 patients refractory to ipilimumab who were enrolled into KEYNOTE 001 and randomised to receive pembrolizumab 2 mg/kg (n=89) every 3 weeks or 10 mg/kg (n=84) every 3 weeks. The authors report that the first 60 patients were randomly assigned in a 2:1 ratio to treatment with pembrolizumab at 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks administered intravenously over 30 min. The sample size was later increased by 100 patients. To achieve a final randomisation ratio of 1:1, the subsequent 100 patients were randomly assigned in a 2:3 ratio to pembrolizumab 2 mg/kg or 10 mg/kg. Any additional patients were randomly assigned in a 1:1 ratio.

This publication reported ORR of 26% for both dosing regimens —21 of 81 patients in the 2 mg/kg group and 20 of 76 in the 10 mg/kg group. Median PFS by independent central review was 22 weeks (95% CI 12–36) for the pembrolizumab 2 mg/kg group and 14 weeks (12–24) for the pembrolizumab 10 mg/kg group (HR 0·84, 95% CI 0·57–1·23. When assessed by the investigator using immune-related response criteria, median PFS was 31 weeks in the pembrolizumab 2 mg/kg group and 35 weeks in the 10 mg/kg group. The Kaplan-Meier estimated overall survival at 1 year (proportion of patients alive at 1 year) was 58% (95% CI 47–68) in the pembrolizumab 2 mg/kg group and 63% (51–72) in the pembrolizumab 10 mg/kg group.

The most common drug-related adverse events of any grade in the 2 mg/kg and 10 mg/kg groups were fatigue (29 [33%] vs 31 [37%]), pruritus (23 [26%] vs 16 [19%]), and rash (16 [18%] vs 15 [18%]). Grade 3 fatigue, reported in five (3%) patients in the 2 mg/kg pembrolizumab group, was the only drug related grade 3 to 4 adverse event reported in more than one patient. Authors concluded that pembrolizumab at doses of 2 mg/kg and 10 mg/kg every 3 weeks had similar and substantial anticancer activity and an acceptable safety profile in patients with advanced melanoma whose disease had progressed on ipilimumab.

KEYNOTE-002: Ribas, Puzanov *et al* (2015)

This was a randomised phase II 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.

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). Patients in the chemotherapy group with documented and verified disease progression at or after week 12 who met the relevant eligibility criteria could cross over to receive pembrolizumab after a washout period of at least 28 days from the last dose of chemotherapy; patients who crossed over were randomly assigned to one of the two pembrolizumab

doses in a double-blind manner. Pembrolizumab was continued until disease progression, unacceptable toxicity, consent withdrawal, physician decision, or other reason.

As of the 12 May 2014 data cut-off date, median follow-up duration was 10 months (IQR 8– 2). Of the 179 patients allocated to the chemotherapy group, 86 (48%) crossed over to pembrolizumab treatment, with 46 randomly assigned to receive 2 mg/kg and 40 to receive 10 mg/kg.

The paper reports that the primary endpoint at the second interim analysis was progression-free survival defined as the time from randomisation to first documented disease progression per RECIST v1.1 by independent central review or death from any cause, whichever occurred first. Secondary endpoints included objective response rate, complete or partial response rates as assessed per RECIST v1.1 by central review, response duration, the time from best overall response of complete or partial response until disease progression; and safety.

Authors reported that based on 410 total progression-free survival events (RECIST v1.1, central review), the study met the pre-specified criteria to show significant improvement in progression-free survival, with hazard ratios (HRs) 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). However, PHARMAC staff note that median progression free survival 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. Pembrolizumab significantly improved progression free survival when assessed by investigator review, with a larger treatment effect for pembrolizumab and a greater separation of the curves. Authors noted that possible investigator bias in this partly open-label trial might explain the greater effect size as compared with central review results.

On independent central review, 38 (21%) patients in the pembrolizumab 2 mg/kg group and 46 (25%) in the 10 mg/kg group responded to treatment as per RECIST v1.1 criteria, compared with eight (4%) in the chemotherapy group (p<0.0001 for each pembrolizumab dose vs chemotherapy).

EORTC QLQ-C30 global health status and quality-of-life scores were similar across all three treatment groups.

The authors considered that although the study was not powered to assess the equivalence of the two pembrolizumab doses, the results do not suggest a significant, clinically meaningful, difference between the doses, therefore the minimally effective pembrolizumab dose of 2 mg/kg given every 3 weeks is recommended for further use.

KEYNOTE-006: *Robert, Schachter et al (2015)*

This was a randomised, 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 enrolled were treatment-naïve). 834 patients were randomised in a 1:1:1 ratio to receive pembrolizumab (at a dose of 10 mg per kilogram of body weight) 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). Pembrolizumab was 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. Patients with confirmed complete responses who received pembrolizumab for at least 6 months could discontinue therapy after receiving at least two doses beyond the determination of complete response. Ipilimumab was administered intravenously over 90-minute period and continued for four cycles or until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, or withdrawal of patient consent.

Primary end points were progression-free and overall survival. Secondary end points included objective response rate (defined as the percentage of patients with complete or partial response according to RECIST criteria), duration of response and safety.

The protocol specified the performance of two interim analyses; the first after at least 260 patients had disease progression or died in all study groups and all patients had been followed for at least 6 months, the second was to be performed after at least 290 patients had died in all the study groups and all patients had been followed for at least 9 months or when the minimum follow-up duration was 12 months, whichever occurred first. After the first interim analysis (data cut-off September 2014) the trial's data and safety monitoring committee reviewed the results and recommended continuing the study as planned and unblinding the results to select representatives of the study sponsor for regulatory purposes. After the second interim analysis (data cut-off March 2015), the data and safety monitoring committee recommended that the study results be un-blinded and pembrolizumab be made available to patients with disease progression in the ipilimumab group. Results presented in the Robert et al publication are from the first interim analysis, except for overall survival, which are from the second interim analysis.

The mean duration of exposure to treatment was 164 days among patients receiving pembrolizumab every 2 weeks, 151 days among those receiving pembrolizumab every 3 weeks, and 50 days for those receiving ipilimumab.

The median duration of follow-up at the time of data cut-off was 7.9 months. At this time point median progression free survival (PFS) 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) in the three arms respectively. The hazard ratios for disease progression for pembrolizumab versus ipilimumab were 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 was not reached in any of the treatment arms, but 1 year survival rates were 74.1%, 68.4% and 58.2 % respectively. One-year estimates of survival were 74.1% for patients receiving pembrolizumab every 2 weeks (hazard ratio (HR) for death as compared with the ipilimumab group, 0.63; 95% CI, 0.47 to 0.83; P<0.0005), 68.4% for those receiving pembrolizumab every 3 weeks (HR for death as compared with the ipilimumab group, 0.69; 95% CI, 0.52 to 0.90; P = 0.0036), and 58.2% for those receiving ipilimumab. Kaplan–Meier Estimates of PFS and OS are shown below:

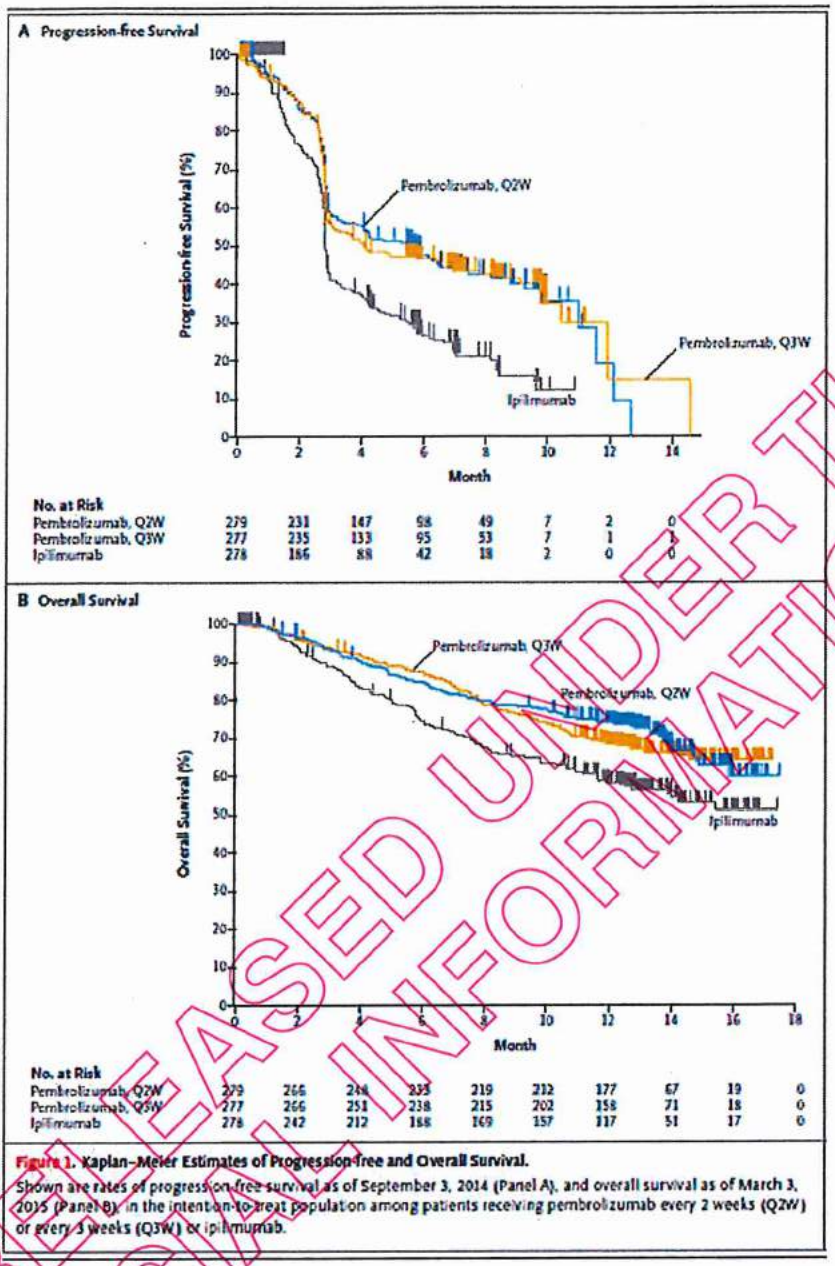


Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.
Shown are rates of progression-free survival as of September 3, 2014 (Panel A), and overall survival as of March 3, 2015 (Panel B), in the intention-to-treat population among patients receiving pembrolizumab every 2 weeks (Q2W) or every 3 weeks (Q3W) or ipilimumab.

Source: Robert, Schachter *et al* (2015)

Regimen	Complete response	Partial response	Stable disease
Pembrolizumab Q2W	5.0%	28.7%	13.3%
Pembrolizumab Q3W	6.1%	26.7%	14.1%

Regimen	Complete response	Partial response	Stable disease
Ipilimumab	1.4%	10.4%	16.5%

The incidence of treatment-related adverse events of grade 3 to 5 severity was lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%). The most common treatment-related adverse events of any grade occurring in the both the pembrolizumab and ipilimumab arms were fatigue, diarrhoea, rash and pruritus. Adverse events on the basis of the likely autoimmune or immune-related mechanism most frequently observed with pembrolizumab were hypothyroidism (10.1% in the 2-week group and 8.7% in the 3-week group) and hyperthyroidism (6.5% and 3.2%, respectively). Grade 3 to 4 events that were reported in more than 1% of pembrolizumab treated patients were colitis (1.4% and 2.5%, respectively) and hepatitis (1.1% and 1.8%, respectively).

Grade 3 to 4 events that were reported in more than 1% of ipilimumab-treated patients were colitis (7.0%) and inflammation of the pituitary gland (i.e. hypophysitis) (1.6%). Hypothyroidism and hyperthyroidism were more frequent in the pembrolizumab groups, whereas colitis and hypophysitis were more frequent in the ipilimumab group.

The authors concluded that pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity than ipilimumab in patients with advanced melanoma.

3 International Recommendations

3.1 Summary of International Economic Analyses

PHARMAC staff searched for evaluations published by international agencies as these may provide useful insights regarding consideration of the supplier's applications for funding in other jurisdictions. PHARMAC staff note that these international recommendations relate to funding legislation, populations, prices, and treatment comparators that are not comparable to the New Zealand situation.

Pharmaceutical Benefits Advisory Committee

The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia recommended at its March 2015 meeting that pembrolizumab be listed for the treatment of treatment naïve unresectable Stage III or Stage IV malignant melanoma at a dose of 2 mg/kg every 3 weeks (Pharmaceutical Benefits Advisory Committee, 2015) .

UK National Institute for Health and Care Excellence

In August 2015 the UK's NICE issued technology appraisal guidance recommending pembrolizumab as an option for treating advanced (unresectable or metastatic) melanoma in adults only after the disease has progressed with ipilimumab and, for BRAF V600 mutation-positive disease, a BRAF or MEK inhibitor (National Institute for Health and Care Excellence, 2015).

NICE is continuing to evaluate pembrolizumab for treating advanced melanoma previously untreated with ipilimumab. The NICE technology appraisal guidance is expected to be published in January 2016.

Scottish Medicines Consortium

The Scottish Medicines Consortium (SMC) in Scotland recommended pembrolizumab as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults who have not been previously treated with ipilimumab, at a dose of 2 mg/g every three weeks.(Scottish Medicines Consortium, 2015)

The SMC does not however recommend use of pembrolizumab in patients previously treated with ipilimumab.

We note that SMC's advice is in the context that there are discounts received via the Patient Access Scheme, which improves the cost effectiveness of pembrolizumab.

3.2 Review of Supplier's Economic Analysis

PHARMAC received an economic evaluation from the supplier, MSD. The following table summarises the PHARMAC staff review and inputs into the supplier's cost-utility analysis.

Model Input/Assumption	Details	PHARMAC Comment
Type of analysis	Cost-utility analysis	Appropriate
Target population	Patients with advanced melanoma who are untreated previously with ipilimumab	Appropriate
Time horizon & cycle length	5 years base, can be run up to 40 years. 1 week cycle length	Lifetime cycle length is recommended by PHARMAC. Weekly cycles are short enough to capture important events.

Model Input/Assumption	Details	PHARMAC Comment
Comparator	Ipilimumab	The appropriate comparator in New Zealand is dacarbazine. As no trials directly comparing pembrolizumab with dacarbazine in the treatment naive population have been reported, an indirect comparison is needed.
Treatment regimen (including dose)	Pembrolizumab dose of 2mg/kg Q3W until disease progression and ipilimumab dose of 3mg/kg Q3W for four cycles	Appropriate
Efficacy	Pembrolizumab efficacy based on results from KEYNOTE-001. The model was built before publication of KEYNOTE-006. Ipilimumab efficacy based on the MDX010-20 trial (Hodi et al 2010)	At the time the model was built this was the most current data. However, this is an indirect comparison with ipilimumab. All valid available evidence was included.
Health states and model structure	Progression free; Post-progression; Death	These states are standard for cancer models. All important states are included. The model is built in MS Excel, which results in it being less transparent than having explicit decision trees and assumptions displayed (eg TreeAGE® software). However, the Excel model is not overly complicated.
Key Assumptions and inputs	Model assumes no dose-response relationship for pembrolizumab. Model assumes that the two trials used are directly comparable. Model assumes cumulative hazard approaches ipilimumab hazard over 40 years. No half-cycle correction included.	Other than the persistence of lower death probability beyond trial end, all assumptions are stated and reasonable. All relevant statistically significant clinical events have been included in the base-case analysis including adverse events. Data incorporated into model appropriately. Probability values calculated appropriately. Cycle length is short enough that half-cycle correction is unneeded.

Model Input/Assumption	Details	PHARMAC Comment
Quality of life	Quality of life weights from Hodi et al EORTC measurements, mapped onto EQ-5D, with UK weights from TA268 (ipilimumab). Sensitivity values from Hodi SF-36 mapped to EQ-5D and Beusterien et al 2009. Adverse events QoL loss included in weights.	Values tested in sensitivity. Utility values used appropriately and implemented correctly in model. New Zealand weights not used.
Pharmaceutical cost	Net Pharmaceutical cost calculated correctly based on proposed rebate and expenditure cap. [redacted]	Pharmaceutical costs calculated appropriately.
Non-pharmaceutical cost	Administration, specialist and palliative care costs have been included. Administration and specialist costs from PHARMAC cost resource manual. Palliative care from BODE^3 calculator. Adverse event costs included. Costs from WEIS NZ and ADHB.	Administration and specialist costs included appropriately. Medical management costs are included but it is not clear what these are and whether scans are included. Distribution costs not included. Palliative care cost included appropriately. WEIS data is taken from DRGs. We note that the cost of grade 3+ dyspnea and endocrine disorders have been assumed to be zero.
Discount rate	3.5%	Appropriate rate used.
Results	Point estimate of [redacted] per QALY	Only point estimate included Model structure and costing is reasonable; however, excludes some costs and comparator is inappropriate.
Sensitivity analysis	Sensitivity analysis done on time horizon, dosage, discount rate and choice of fitting.	Discount rate sensitivity is appropriate and done as specified in the PFPA.
Report	Report is relatively thorough. Explanation of the derivation of some costs is missing.	Comparator is different from that used in New Zealand.

4 Economic Analysis

4.1 Scope of Analysis

4.1.1 Decision Problem and Perspective

PHARMAC staff have undertaken a preliminary cost-utility analysis to estimate the cost per QALY of funding pembrolizumab for patients with unresectable or metastatic (Stage III and IV) melanoma. The levels of analysis are described in the Prescription for Pharmacoeconomic Analysis (PFPA).

This analysis was conducted from perspective of the funder, with regards to PHARMAC's Decision Criteria.

4.1.2 Target Population

The target population for this analysis was defined as treatment naïve patients with unresectable or metastatic (Stage III and IV) melanoma.

4.1.3 Comparator

PHARMAC staff are not aware of any trials (reported or registered) comparing pembrolizumab with dacarbazine in the treatment naive unresectable or metastatic (Stage III and IV) melanoma population Therefore, the comparators used in the analysis are dacarbazine and ipilimumab. Although ipilimumab is not funded in New Zealand, it has been used as an intermediate comparator treatment to enable indirect comparison between dacarbazine and pembrolizumab. The workings and results are described in section 4.2.4 below.

4.2 Economic Model

A Markov model has been constructed to model the different treatment strategies. This model uses data derived from KEYNOTE-006 which indicated improvement in both progression-free survival and overall survival for pembrolizumab over ipilimumab as explained in this section.

4.2.1 Time Horizon

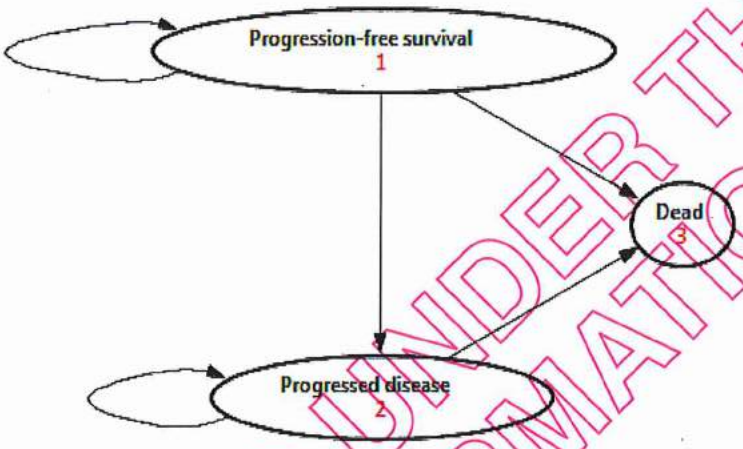
The time-horizon of the CUA is 40 years. This was chosen as it is significantly beyond the life expectancy of the patient population. Each Markov cycle was 3 weeks, as all three treatments (dacarbazine, ipilimumab and pembrolizumab) are administered as 3-weekly treatment cycles. All costs and benefits have been discounted at 3.5% as specified in the PFPA.

4.2.2 Model Structure

The Markov model included the following health states:

- Progression-free survival;
- Progressed disease;
- Death

A branch of the Markov model is included below:



4.2.3 Key Assumptions and Inputs

It is assumed that patients whose disease progresses whilst receiving treatment with pembrolizumab do not recover. It is also assumed that 50% of patients whose disease progresses whilst receiving treatment with pembrolizumab will receive subsequent treatment with dacarbazine. As this variable is uncertain, it has been tested heavily in sensitivity. We have used data from KEYNOTE-006 which used 10mg/kg dosing. However, we have assumed that 10mg/kg dosing has the same efficacy as the 2mg/kg registered dose.

4.2.4 Transformation and Extrapolations

PHARMAC staff are not aware of any trials (reported or registered) comparing pembrolizumab with dacarbazine in the treatment naive unresectable or metastatic (Stage III and IV) melanoma population. Therefore our analysis has used the hazard ratios for pembrolizumab to ipilimumab from KEYNOTE-006, and then applied the hazard ratios for ipilimumab to dacarbazine from (Robert, Thomas *et al*, 2011). These hazard ratios are shown in the table below:

Event	Pembrolizumab vs ipilimumab	Ipilimumab vs dacarbazine	Pembrolizumab vs dacarbazine
Progression	0.57	0.76	0.433
Death	0.69	0.72	0.497

The reason that hazard ratios have been used instead of directly using the Kaplan-Meier survival curves is that the ipilimumab control arm in KEYNOTE-006 had a significantly higher survival rate than has been observed in previous ipilimumab trials including (Robert, Thomas *et al*, 2011). This made direct comparison using the Kaplan-Meier survival curves likely to overstate the benefit of pembrolizumab.

4.3 Health-Related Quality of Life

The utility values included in the analysis were obtained using the New Zealand EQ-5D. Health state descriptions were informed by PTAC and CaTSoP members, and the supplier's analysis. PHARMAC staff note that symptoms in Stage 4 melanoma can vary widely: "When stage 4 melanoma is diagnosed after a scan, there may be no symptoms at all, and it can be difficult to believe the cancer has spread. However, people with stage 4 melanoma may have a very wide range of symptoms" (British Association of Dermatologists, 2015).

NZ tariff-2 EQ-5D weights were applied to the generic health states to derive quality of life scores. The EQ-5D scoring of the states and the corresponding quality of life weights are given in the following table, and compared with the patient-reported weights collected in the supplier's application

Health State	EQ-5D scores	Utility NZ Tariff 2
Progression-free survival	11(1-2)11	0.801
Progressed disease	(1-2)(1-2)222	0.5375

The supplier application also included different patient-reported quality of life weights, as below:

Utility from Hodi EORTC (sd)	Utility from Hodi SF-36 (sd)	Beusterien et al 2009 (sd)
0.801 (0.138)	0.640 (0.118)	Partial response[iii]: 0.88 (0.01) Stable disease: 0.80 (0.01)
0.763 (0.160)	0.619 (0.130)	0.52 (0.02)

[iii] Complete response was not included in this study

The modelled weights of 0.8 and 0.5375 for the progression-free and progressed disease states are very similar to the European Organisation for Research and Treatment of Cancer (EORTC) results for ipilimumab reported by Hodi, O'Day *et al* (2010).

Hodi, O'Day *et al* (2010) also reported utility weights derived from the SF-36. The potential health gain, as measured by the difference between the weights for the progression-free and progressed disease health states, is much smaller than the potential health gain as measured by the EQ5D-3L with the New Zealand population preferences.

Beusterien, Szabo *et al* (2009) reported on utilities for advanced melanoma reported by members of the general public in Australia and the United Kingdome. The values were elicited directly using the standard gamble technique. While its results are not strictly directly comparable to the EQ-5D weights using the New Zealand tariff, the study did find very similar values to the ones we have used in this model.

4.4 Costs

4.4.1 Pharmaceutical Costs

The following pharmaceutical costs were included in the analysis:

Item (dose per cycle)	Price per vial	Vials per 3-week cycle	Net average cost per 3-week cycle
Pembrolizumab (2mg/kg)	[redacted]	3.41	[redacted]
Ipilimumab (3mg/kg)	[redacted]	5.29	[redacted]
Dacarbazine (1000mg/m^2)	[redacted]	5	[redacted]

We note that doses used in the clinical trials for pembrolizumab were conducted over a range including 2mg/kg every 3 weeks, 10mg/kg every two weeks and 10mg/kg every 3 weeks. In our analysis we have assumed the doses listed in section 1.7 above based on the Medsafe-approved dosing schedule, with each treatment administered at the beginning of a 3 weekly cycle. Similarly we have assumed the Medsafe-approved doses for ipilimumab and dacarbazine.

We have included 10% wastage on the pharmaceutical price to account for using of whole vials. Further, third-party compounding services charge a 5% mark-up on the list price. We have assumed that approximately half the patients will have their treatment compounded by the administering DHB in-house, and thus these do not attract a 5% mark-up.

The pembrolizumab average cycle cost is based on a net per vial average price of [redacted] assuming that the net expenditure over 5 years reaches the proposed net expenditure cap. This was calculated as a weighted average across the 5 year period. If net expenditure does not reach the proposed cap in the 5 year period, the net per vial price is assumed to be [redacted] Details of this calculation are in section 5. A scenario of volumes falling short of the cap has been included in sensitivity analysis. The supplier's analysis assumes that expenditure reaches the cap in year 3.

[iv] List price times average dose

4.4.2 Health Sector Costs

Infusion costs were estimated using data from PHARMAC's cost resource manual as at November 2015.

		Quantity used per cycle of treatment		
Admin Factor	General Cost	Pembrolizumab	Ipilimumab	Dacarbazine
Bed time	$65 per hour	0.5	1.5	0.25
Nurse time	$42 per hour	0.5	1.5	0.25
Dispensing	$50 per hour	0.25	0.25	0.25
Compounding Charge	$20 per dose	1	1	1
Oncologist time	$250 per attendance	1	1	1
CT scan	$650 per scan[v]	0.25	0.25	0.25

Administration costs refer to the marginal unit of time used to administer the pharmaceutical. We note that there is the potential that DHB hospital infusion services may not currently have the capacity to administer pembrolizumab to all potential patients with unresectable or metastatic melanoma stage III or IV potentially eligible for funded pembrolizumab in the event that it is listed on the Schedule. However, for the base case, we have assumed that DHB outpatient clinics would be able to meet all demand for infusion services. Also, we note that the DHB prices listed in the Cost Resource Manual include all overheads including capital charges.

We note that the initial Special Authority access criteria proposed by the supplier are valid for a maximum of 4 cycles (12 weeks), and that renewal applications would be required every 3 months thereafter, ie, every 4 cycles. The renewals would have to state that radiological assessment (preferably including CT scan) indicates melanoma has not progressed. Our analysis assumes that CT scans are performed every 4 cycles to determine whether the patient's disease has not progressed and therefore eligibility for ongoing funded treatment. Staff consider that, given scans would be performed only after every 4th cycle, there is potential for patients to receive treatment beyond actual disease progression. Therefore, our analysis includes a correction of an average of 2 cycles of additional costs for when patients transition from PFS to progressed disease to account for the average time from actual disease progression to next CT Scan, reporting of results and subsequent discontinuation of treatment.

We have used the supplier's modelled terminal care cost of [redacted] which is applied when patients transition from either of the alive states (progression free survival and progressed disease) to death. The supplier's terminal care cost is the figure published by the University of Otago's BODE[3] group, derived from the Ministry of Health's Health Tracker analysis of cancer treatment costs.

[v] Taken from the sunitin b TAR

4.5 Results of Economic Analysis

The preliminary economic analysis indicates a base case cost-effectiveness estimate of pembrolizumab for the treatment of patients with unresectable or metastatic melanoma stage III or IV of approximately [redacted]

The estimated incremental costs and QALY gains in the base-case analysis are included in the table below.

Strategy	Cost average per person (discounted)	Incr Cost	QALY (per person, discounted)	Incr QALY	Cost per QALY (per person, discounted)	QALYs gained per $million
Pembrolizumab	[redacted]	[redacted]	1.24	0.62	[redacted]	[redacted]
Dacarbazine	[redacted]		0.62			

Note that as we have modelled a lower progression-free survival than the supplier has, the time on treatment in our model is also lower, which decreases the modelled incremental cost of pembrolizumab.

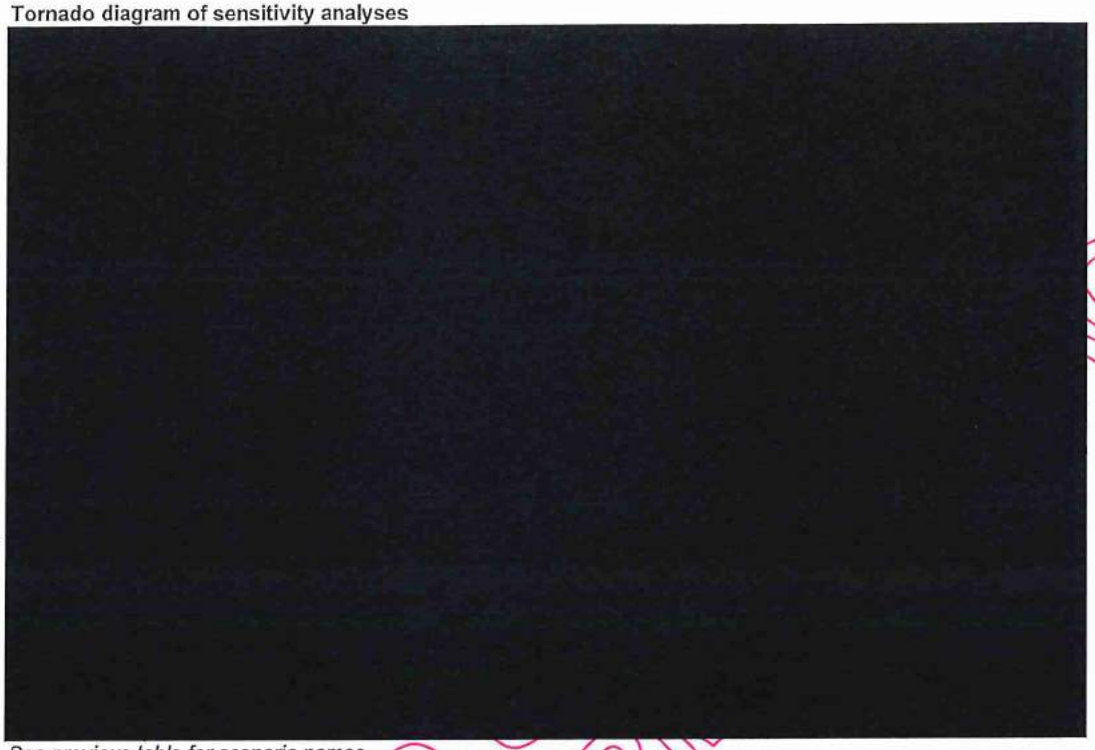
4.6 Sensitivity Analysis

We have undertaken several sensitivity analyses, testing key variables across plausible ranges. As well, we have tested structural parameters such as different patient numbers, and the number of vials used per cycle.

All hazard ratio variables were tested to their 95% confidence intervals. The "extra rebate due to cap" scenario (3) reflects what would happen if the proposed expenditure cap is not reached. As there is significant uncertainty about patient numbers, this results in uncertainty in the average cost per patient.

Input (Scenario number)	Base case	Low value	High value	Cost per QALY ($000s)	QALYs gained per $million
HR for death of pembrolizumab compared with ipilimumab (1)	0.69	0.52	0.9	[redacted]	[redacted]
Utility weight of progressed disease (2)	0.5375	0.2	0.763	[redacted]	[redacted]
Extra rebate per vial due to cap (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR for death on ipilimumab compared with dacarbazine (4)	0.72	0.588	0.87	[redacted]	[redacted]
PFS on dacarbazine (weeks) (5)	12	6	18	[redacted]	[redacted]
OS on dacarbazine (weeks) (6)	38	25	60	[redacted]	[redacted]
Utility weight of PFS (7)	0.801	0.5	1.0	[redacted]	[redacted]
Average vials used per cycle (8)	3.41	3	4	[redacted]	[redacted]
Number of cycles between progression and treatment end (9)	4	2	8	[redacted]	[redacted]
Cost of medical management in PFS state (10)	$412.50	$0	$1800	[redacted]	[redacted]
HR for progression of pembrolizumab compared with ipilimumab (11)	0.57	0.47	0.72	[redacted]	[redacted]
HR for progression of ipilimumab compared with dacarbazine (12)	0.76	0.63	0.93	[redacted]	[redacted]
Cost of scan (13)	$650	$0	$2000	[redacted]	[redacted]
Cost of adverse event management per cycle (14)	$0	$0	$1000	[redacted]	[redacted]
Discount rate (15)	3.5%	0%	5%	[redacted]	[redacted]
Mark-up (16)	[redacted]	0%	[redacted]	[redacted]	[redacted]
Cost of medical management in the progressed state (17)	$170	$0	$340	[redacted]	[redacted]
Cost of specialist appointment (18)	$250	$100	$450	[redacted]	[redacted]
Proportion of people treated with dacarbazine after progression (19)	50%	0%	100%	[redacted]	[redacted]
Cost of a vial of dacarbazine (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average cycles of post-progression dacarbazine (21)	5	3	7	[redacted]	[redacted]
Cost of palliative care (22)	$6,159	$0	$15,000	[redacted]	[redacted]

Tornado diagram of sensitivity analyses



See previous table for scenario names

5 Budget Impact Analysis

PHARMAC staff note that the New Zealand Cancer Registry has records for the numbers of newly diagnosed melanoma and number of deaths attributed to melanoma up until 2012. However, due to the Registry not capturing information on the progression of melanoma from one stage to another, we have used mortality figures as a surrogate for the likely number of patients eligible for treatment with pembrolizumab each year. That means that we have assumed that all those who die of melanoma have late stage disease. PHARMAC staff estimate this figure to be approximately 380 patients in the year to June 2016.

To be consistent with the supplier's proposed expenditure cap, for the purposes of this analysis we have assumed a listing date of April 2016. We further assume that there would be an additional bplus/backlog of 20% of estimated first year patients who are currently accessing treatment (privately or through compassionate access/clinical trials) that would commence funded treatment in fiscal year 1.

We assume that 60% of people who commence funded treatment with pembrolizumab would remain on treatment after 4 cycles until disease progression or unacceptable toxicity. This proportion is based on data from the KEYNOTE006 trial and includes those people who respond to treatment, either completely or partially, and those whose disease is stable whilst on pembrolizumab treatment. The median duration of treatment until disease progression for patients with responsive disease in KEYNOTE-006 was 28 three weekly cycles and therefore we have assumed that for these patients the median time on treatment would be 20 months.

The analysis also assumes that those who do not respond to treatment would cease treatment after 4 cycles, as under the supplier's proposed access criteria these patients would not be eligible for an additional 4 cycles (3 months) ongoing funded pembrolizumab treatment.

There is significant uncertainty about the number of potentially eligible patients and the rate at which potentially eligible patients would commence pembrolizumab treatment. There is also uncertainty about whether current infusion services in DHB hospitals would have the capacity to administer pembrolizumab for the number of additional patients estimated to be eligible for funded access to this treatment.

The supplier has proposed an indicative confidential rebate of [redacted] per vial as well as a net expenditure cap of [redacted] each year. This means that PHARMAC would be able to claim all additional net CPB expenditure above the proposed cap back from MSD. MSD has indicated to PHARMAC that its current commercial proposal terms proposed in its funding application are 'illustrative', and that the final expenditure figure is likely to change depending on the access criteria and eligible patient population.

Pharmaceutical Cancer Treatments listed in the Pharmaceutical Schedule administered by IV infusion are claimable at a price per mg that typically includes a [redacted] mark-up to account for wastage when extemporaneously compounded by a third party provider. This cost has been included in the budget impact analysis. We estimate that 50% of New Zealand patients would have their cancer treatments compounded by a third party provider with the remainder receiving treatment that has been compounded by the DHB in-house. The service fees and mark-ups charged by third party compounders have been included in the analysis.

We estimate that the approximate financial impact of funding pembrolizumab is as follows:

Proposal year	1 (3 months)	2	3	4	5
Financial year ending	30-Jun-16	30-Jun-17	30-Jun-18	30-Jun-19	30-Jun-20
Patients	85	382	341	349	356
Gross cost to CPB before rebates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost to CPB after rebates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net distribution costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost DHBs (excl sector offsets)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total net additional sector costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total net cost DHBs (incl sector costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note that the above budget impact analysis assumes that all eligible patients will receive treatment, and does not take into account potential service constraints such as infusion services reaching full capacity, limited access to oncologists, or limited access to scans.

We estimate that the budget impact of listing pembrolizumab will cost DHBs approximately [redacted] in the first full year, growing to approximately [redacted] in the fifth year. The 5 year NPV, discounted at 8%, is approximately [redacted]

6 Discussion

This is a preliminary assessment as defined in version 2.2 of the Prescription for Pharmacoeconomic Analysis (PFPA). It is intended to inform PHARMAC's prioritisation of possible options for investment.

Clinical trials show pembrolizumab may have some early benefits; however we note that at this time the long term benefits and risks are not clear. Preliminary analysis indicates that the cost-effectiveness of pembrolizumab may be in the range of [redacted] invested (with a point estimate of [redacted]) noting that this result is dependent on a number of highly uncertain variables including the number of patients with metastatic or unresectable stage III or IV melanoma in New Zealand that would access treatment, the duration of treatment and the benefit patients receive from treatment. It is important to note that under the suppliers proposed commercial proposal, that includes a net expenditure cap, pembrolizumab becomes more cost effective as more patients are treated and as duration of treatment increases. If fewer patients access treatment, if the treatment does not deliver the benefits seen in the early data analyses, or if the benefits in the clinical trials are not realised in normal clinical practice, the cost effectiveness of the treatment would decrease.

We estimate that the budget impact of funding pembrolizumab treatment for patients with unresectable or metastatic stage III or IV melanoma to be approximately [redacted] depending on the rate of uptake and factoring in the supplier's proposed commercial terms of a confidential rebate and indicative net expenditure cap each year.

We note that our analysis indicates annual net costs would exceed the supplier's proposed net expenditure cap 15 months from the initial listing date and that the presence of a 'hard' expenditure cap, where sales over the cap are 'free', means that an increase in estimated patient numbers or the estimated rate of uptake has the effect of reducing the average net price per vial and so the average pharmaceutical cost per patient treatment cycle. There is significant uncertainty around patient uptake and infusion capacity which means that this assumption is not reliable.

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Technology Assessment Report 271a – Update for pembrolizumab for metastatic or unresectable melanoma stage III or IV

July 2016

This assessment updates the December 2015 estimate of the likely cost-effectiveness range of pembrolizumab for advanced melanoma. This TAR is a supplement to TAR 271, and describes the changes that were made to the economic model to bring it in line with the model for nivolumab described in TAR 274.1.

1. Pharmaceutical cost

The net price per vial of pembrolizumab has been updated to the effective price to be considered by the PHARMAC Board on 29 July, which is [redacted].

2. Model structure

Since December 2015, the economic model for immunotherapy for advanced melanoma has been updated in light of new information. Full details of the updates are documented in in TAR 274.1; the key changes are:

- The cycle length has been reduced to 1 week
- The probability of death is reduced after 100 cycles
- A state of "off treatment but not progressed" has been added to allow the modelling of patients who discontinue treatment due to adverse events.

All other variables remain the same, including the use of dacarbazine as the comparator, and all measures of clinical effectiveness.

3. Results

TAR 271 estimated the cost-effectiveness of pembrolizumab compared to dacarbazine for advanced melanoma to be [redacted] with a likely range of [redacted] per $million.

The revised analysis is below.

Strategy	Cost average per person (discounted)	Incr Cost	QALY (per person, discounted)	Incr QALY	Cost per QALY (per person, discounted)	QALYs gained per $million
Pembrolizumab	[redacted]	[redacted]	2.25	1.32	[redacted]	[redacted]
Dacarbazine	[redacted]		0.93			

The likely range for the cost effectiveness of pembrolizumab compared to dacarbazine for advanced melanoma is now estimated to be [redacted] with a likely range of [redacted]

4. Sensitivity analysis

Note that while clinical advice is that pembrolizumab and nivolumab are clinically equivalent, the adjusted hazard ratios in the key clinical trials differ (though not statistically significantly). If the hazard ratios from the key nivolumab trial is used, the cost-effectiveness will be [redacted]. Note that this is within the likely range displayed above.