PTAC meeting held on 5 & 6 May 2016

(minutes for web publishing)

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

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

PTAC may:

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

1. Nivolumab for advanced melanoma

Application

1.1 The Committee considered an application from Bristol-Myers Squibb (NZ) Ltd (BMS) for the new listing of nivolumab (Opdivo) as monotherapy, and as a combination with ipilimumab (Yervoy), for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma.

Recommendation

1.2 The Committee recommended that nivolumab as monotherapy be funded with medium priority for the treatment of patients with metastatic or unresectable Stage IIIc or Stage IV melanoma.

1.3 The Committee recommended that the application for nivolumab as a combination with ipilimumab for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma be declined.

1.4 The Committee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

1.5 The Committee noted that New Zealand has the highest incidence of melanoma in the world and a high mortality rate. The Committee considered that there is a high unmet health need for effective treatments for patients with advanced melanoma.

1.6 The Committee noted the age standardised mortality rates of melanoma in New Zealand (Sneyd and Cox BMC Cancer 2013, 13:372); The Committee also noted that the international five-year survival data for treated patients with advanced melanoma is 40% for stage IIIc disease and 15%–20% for stage IV disease and the ten-year survival is 24% and 10%–15%, respectively, as reported at: http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-survival-rates.

1.7 The Committee noted that it had previously considered applications for a number of treatments for advanced melanoma, including proto-oncogene BRAF and mitogen activated protein kinase enzyme (MEK) inhibitors, and antibodies that inhibit cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1).

1.8 The Committee noted that nivolumab is a fully human IgG4 monoclonal antibody immune checkpoint PD-1 inhibitor. The Committee noted that PD-1 is a protein expressed on T-cells that transmits co-inhibitory signals upon engagement with the tumour-expressed ligands PD-L1 and PD-L2. The Committee noted that the PD-1 system is pivotal in the regulation of autoimmunity, transplantation immunity, infectious immunity, and tumour immunity. The Committee also noted that, due to the phase of the PD-1 interaction in T-cell response to tumours, PD-1 inhibitors may result in fewer adverse events than with inhibition of CTLA-4 such as occurs with ipilimumab.

1.9 The Committee noted that the recommended dose for nivolumab as monotherapy is 3 mg/kg every 2 weeks administered intravenously over 60 minutes until disease progression or significant adverse effects, although published studies have not continued treatment for longer than 96 weeks.

1.10 The Committee noted that for treatment in combination with ipilimumab the recommended dose is nivolumab 1 mg/kg infused over 60 minutes followed by ipilimumab 3 mg/kg infused over 30 minutes every three weeks for the first four doses, followed by nivolumab 3 mg/kg every 2 weeks until disease progression or significant adverse effects.

1.11 The Committee noted that the application had been considered by the Cancer Treatments Subcommittee of PTAC (CaTSoP) at its April 2016 meeting, at which the Subcommittee recommended nivolumab as monotherapy be funded with medium/high priority for the treatment of patients with metastatic or unresectable Stage IIIc or Stage IV melanoma. The Committee noted that CaTSoP had deferred making a recommendation regarding combination treatment as the Subcommittee had considered the currently available evidence too immature to draw meaningful conclusions.

Nivolumab monotherapy

1.12 The Committee noted evidence for the use of nivolumab monotherapy from a phase I study designed to assess the safety, anti-tumour activity and pharmacokinetics of nivolumab in 296 patients with various solid tumours including melanoma, non-small cell lung cancer, prostate cancer, renal cell carcinoma and colorectal cancer (Topalian et al. N Eng J Med 2012;366:2443-54).

1.13 The Committee noted that, of the 94 patients with melanoma in the trial, 28% had objective responses at doses ranging from 0.1 mg/kg to 10 mg/kg every 2 weeks, with the highest response rate (41%) observed at a dose of 3 mg/kg.

1.14 The Committee noted that responses appeared durable, as long term follow up of 107 patients with advanced melanoma from this trial reported overall response rates (ORR) of 31% with a median response duration of 2 years (Topalian et al J Clin Oncol 2014;32:1020). With a median follow-up of 16.8 months, the one and two-year survival rates in the trial were 62% and 43%, respectively; one and two year progression free survival (PFS) rates were 36% and 27%, respectively, with a median PFS of 3.7 months (Topalian et al J Clin Oncol 2014;32:1020).

1.15 The Committee noted that further follow-up data from this phase 1 study were presented at the American Association for Cancer Research (AACR) Annual Meeting in April 2016, where it was reported that the 60-month overall survival (OS) rate of patients who had received up to 96 weeks of treatment, was 34% (95% CI: 25-43%) and median OS was 17.3 months (95% CI: 12.5-37.8 months) (Hodi et al. AACR 2016, Abstract CT001).

1.16 The Committee noted evidence from another phase I study of nivolumab at 1, 3 or 10 mg/kg every 2 weeks for 24 weeks, then every 12 weeks for up to 2 years with or without multipeptide vaccine in 90 patients with ipilimumab-refractory or ipilimumb-naive unresectable stage III or IV melanoma (Weber et al. JCO 2013;31:4311-18). The Committee noted that the ORR was 26% and 24% for ipilimumab-refractory and ipilimumab-naïve patients, respectively, and the addition of the vaccine did not improve clinical efficacy.

1.17 The Committee noted evidence from CheckMate-037, a phase III randomised, controlled, open-label trial comparing nivolumab (3 mg/kg every two weeks) with investigator choice of chemotherapy (dacarbazine or paclitaxel/carboplatin) in 405 patients with advanced melanoma who had progressed on ipilimumab or ipilimumab and a BRAF inhibitor (Weber et al. Lancet Oncol 2015;16:375-384).

1.18 The Committee noted that, with a median follow-up of 8.4 months, objective responses in the trial were observed in 31.7% of patients in the nivolumab arm compared with 10.6% in the chemotherapy arm. The Committee noted that grade 3 and 4 treatment-related adverse events occurred in 9% of patients in the nivolumab arm and 31% in the chemotherapy arm. The Committee noted that no significant difference in six-month PFS between study arms was reported.

1.19 The Committee considered the findings of CheckMate-066, a phase III, randomised, controlled, double-blind study of nivolumab monotherapy compared with dacarbazine in 418 patients with previously untreated metastatic melanoma without a BRAF mutation (Robert et al N Eng J Med 2015;372:320-30). The Committee considered that, although this study did not include any New Zealand centres, the patients would be representative of a New Zealand population.

1.20 The Committee noted that patients in the trial were randomised 1:1 to receive intravenous infusion of either nivolumab 3 mg/kg every 2 weeks and dacarbazine-matched placebo every 3 weeks (n=210) or dacarbazine 1000 mg/m2 every 3 weeks and nivolumab-matched placebo every 2 weeks (n=208) until disease progression or unacceptable toxicity. The Committee noted that patients were stratified by PD-L1 status and metastasis stage and that treatment could continue after disease progression if the patient was experiencing clinical benefit.

1.21 The Committee noted that the study was unblinded in June 2014, following an interim database lock, and the protocol was amended to allow patients enrolled in the dacarbazine arm to receive nivolumab due to a significant difference in OS in favour of nivolumab.

1.22 The Committee noted that the ORR results from the double-blind portion of the study were 40.0% (95% CI 33.3-47.0) for the nivolumab arm compared to 13.9% (95% CI 9.5-19.4) in the dacarbazine arm (Odds Ratio for ORR 4.06 (95% CI 2.52-6.54), p<0.001) as measured by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

1.23 The Committee noted that the median PFS at one year was 5.1 months in the nivolumab arm versus 2.2 months in the dacarbazine arm (HR 0.43, 95% CI 0.34-0.56, p<0.001) and OS at one year was 72.9% (95% CI 65.5-78.9) and 42.1% (95% CI 33.0-50.9), respectively (HR 0.42, 99.79% CI 0.25-0.73, p<0.001). The Committee noted that the CI for the HR of OS was adjusted on the basis of a Type I error rate adjustment for interim analyses. The Committee noted that the survival advantage with nivolumab was seen across all pre-specified subgroups and occurred independent of PD-L1 status.

1.24 The Committee noted that the most common treatment-related adverse events reported in the nivolumab arm were fatigue (20%), pruritus (17%), nausea (17%), diarrhea (16%) and rash (15%). The Committee noted that treatment-related adverse events of any grade were 74.3% in the nivolumab arm and 75.6% in the dacarbazine arm; however, grade 3 or 4 adverse events occurred in only 11.7% and 17.6% of patients in the nivolumab and dacarbazine arms, respectively.

1.25 The Committee noted that an updated survival analysis had been presented at Society for Melanoma Research (SMR) Congress in 2015. The Committee noted that with a median follow up of 18.5 months in the nivolumab arm and 10.9 months in the dacarbazine arm, 38% of patients in the nivolumab arm and 67% in the dacarbazine arm had died (Atkinson et al SMR 2015 poster presentation). The Committee noted that median OS had not been reached in the nivolumab arm and was 11.2 months in

the dacarbazine group, HR 0.43 (95% CI; 0.33 to 0.57, p<0.001). The Committee noted that estimated two year OS rates were 58% and 27% for the nivolumab and dacarbazine arms, respectively.

1.26 The Committee considered that the phase III evidence for the use of nivolumab as monotherapy was of good strength and quality with randomised, placebo controlled double-blind trial design and use of a comparator appropriate in the New Zealand setting.

1.27 The Committee considered that the evidence for nivolumab monotherapy provided a strong level of support for a survival benefit for patients with advanced melanoma over the current standard of care in New Zealand, but noted that the data were still immature with regards to long-term survival.

1.28 The Committee considered that from the currently available evidence, the maximum duration of treatment in a responding patient was uncertain. The Committee noted that, to date, 96 weeks is the maximum treatment duration reported in studies.

1.29 The Committee considered that currently available evidence was consistent with 34% five-year survival, but because the maximum treatment duration reported in the trials was limited to 96 weeks, that it was uncertain if this would still be the case as more evidence was published. The Committee considered that prolonging treatment after 96 weeks in responders means it was difficult to give advice about the fiscal risk of funding this treatment, as long-term responders could continue to receive nivolumab as long as they could still tolerate it, but that there was a lack of current evidence that continuing treatment would provide further benefit.

1.30 The Committee considered that a biomarker that enabled treatment to be targeted to those patients who would most benefit may become available in the future, but also considered that the evidence did not currently support the use of PDL1 in targeting treatment.

1.31 The Committee considered that nivolumab as monotherapy should be funded for the treatment of patients with metastatic or unresectable Stage IIIc or Stage IV melanoma, based on the strength and quality of the evidence and the unmet health need of the patient population, but noted the high cost and uncertainty about this cost into the future.

Nivolumab in combination with ipilimumab

1.32 The Committee noted the findings of a phase I study of 86 patients with advanced melanoma treated either with concurrent of sequential nivolumab and ipilimumab (Wolchock et al N Eng J Med 2013;369:122-33). The Committee noted that 40% of patients treated with concurrent therapy had objective responses (95% CI 27% to 55%). The Committee noted that 16 patients had tumour reduction of 80% or more by week 12.

1.33 The Committee noted the findings of CheckMate-069, a phase II, double-blind randomised study involving 142 patients with previously untreated metastatic melanoma and known BRAF V600 mutation status randomly assigned 2:1 to receive ipilimumab 3 mg/kg combined with either nivolumab 3 mg/kg or placebo every two weeks until disease progression or unacceptable toxicity (Postow et al. N Eng J Med Med 2015;372:2006-1). The published study report stated that the minimum study follow-up at database lock was 11 months.

1.34 The Committee noted in the PFS plot that after six months 54/109 (49.5%) of participants were still at risk of an event. Median PFS was not reached in the combination group but was 4.4 months in the ipilimumab monotherapy group. The reported ORR among BRAF wild-type tumours was 61% in the combination group and 11% in the ipilimumab only group. The Committee noted that among patients with BRAF V600 mutation-positive tumours, ORR was 52% in the combination group and median PFS was 8.5 months in the combination group and 2.7 months in the ipilimumab monotherapy group. The Committee considered that nivolumab appears to work irrespective of BRAF mutation status.

1.35 The Committee noted that updated survival data from this study were presented at the AACR April 2016 meeting (Postow et al AACR 2016, Abstract CT002), where it was reported that, at 18 months follow up, OS rates in BRAF wild-type patients were 73% in the combination arm and 56% in the ipilimumab monotherapy arm, and median OS had not been reached in either group (HR 0.56; 95% CI 0.29-1.10; p=0.089)

1.36 The Committee noted the results of CheckMate-067, a phase III, randomised, double-blind, placebo-controlled study comparing nivolumab alone (3 mg/kg every 2 weeks); nivolumab (1 mg/kg every 3 weeks) plus ipilimumab (3 mg/kg every 3 weeks) for four doses followed by nivolumab alone; or ipilimumab alone (3 mg/kg every 3 weeks) in 945 treatment naive patients with unresectable stage III or IV melanoma (Larkin et al. N Engl J Med 2015; 373:23-34). The Committee noted that patients were stratified by tumour PDL1 status, BRAF mutation status, and disease stage.

1.37 The Committee noted that, at a median follow-up of 12 months, ORRs were 43.7% in the nivolumab group, 57.6% in the combination group and 19% in the ipilimumab group. Members noted that 8.9% of patients in the nivolumab group achieved complete response compared to 11.5% in the combination group and 2.2% in the ipilimumab group.

1.38 The Committee noted that median PFS was 6.9 months (95% CI, 4.3-9.5) in the nivolumab group, 11.5 months (95% CI, 2.8-3.4) in the combination group and 2.9 months (95% CI 2.98-3.4) in the ipilimumab group. The hazard ratio for death or disease progression was 0.42 (99.5% CI, 0.31 to 0.57; P<0.001) for the combination group against ipilimumab only.

1.39 The Committee noted that the incidence of grade 3 or 4 treatment-related adverse events was 16.3% in the nivolumab group, 55% in the combination group and 27.3% in the ipilimumab group. The Committee noted that 83% of patients in the combination group required immunomodulatory agents compared with 47% in the nivolumab group and 56% in the ipilimumab group.

1.40 The Committee considered that the currently available data for combination treatment indicate that it may offer superior efficacy but was associated with greater toxicity when compared with treatment with a CTLA-4 inhibitor or PD-1 inhibitor alone. Members also considered that the data were still immature with regards to long-term survival.

1.41 The Committee considered that the application for nivolumab in combination with ipilimumab should be declined, based on immaturity of the currently available data for combination treatment, a significant adverse effect profile, and the extremely high price being sought by the supplier. The Committee considered that the application should be reconsidered following publication of longer-term survival and toxicity data.

General Comments

1.42 The Committee noted that the currently available evidence is consistent with different PD-1 inhibitors (i.e. pembrolizumab and nivolumab) having similar efficacy, however, noted there appears to be no head-to-head studies. The Committee considered that it was not presented with any particular safety or efficacy concerns associated with patients switching between one PD-1 inhibitor and another, but this was an area of uncertainty.

1.43 The Committee considered that if a new treatment for advanced melanoma was listed on the Pharmaceutical Schedule that in the first year of use the number of patients accessing this therapy would likely be double that accessing therapy in subsequent years. Members considered that this could cause significant capacity issues for hospital infusion services.