Cancer Treatments Subcommittee of PTAC
Meeting held 22 April 2016

(minutes for web publishing)

Cancer Treatments Subcommittee 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 Cancer Treatments Subcommittee (CaTSoP) meeting; only the relevant portion of the minute relating to CaTSoP's discussion about the application for nivolumab (Opdivo). This document will be updated in due course.

The Cancer Treatment Subcommittee may:

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

This Subcommittee minute was reviewed by PTAC at its meeting 5 & 6 May 2016. The record of the PTAC meeting will be made available on the PHARMAC website as soon as it is finalised.

1 Nivolumab for advanced melanoma

Application

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

Recommendation

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

1.3 The Subcommittee has taken into account, where applicable, PHARMAC's current decision-making framework as appropriate in relation to its advice for this recommendation.

1.4 The Subcommittee deferred making a recommendation on the application for nivolumab in combination with ipilimumab for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma, as the Subcommittee considered that the currently available evidence is too immature to draw meaningful conclusions.

Discussion

1.5 The Subcommittee noted that New Zealand has the highest incidence of melanoma in the world and between 1998 and 2008 the incidence has risen 12% in men and 16% in women. Members noted that, in New Zealand, overall survival rates were poor for patients with Stage IV disease with the currently available funded treatments - radiation, surgery, immunotherapy, or chemotherapy (dacarbazine). The Subcommittee considered that there is a high unmet health need for effective treatments for patients with advanced melanoma.

1.6 The Subcommittee noted that the supplier was requesting funding for both nivolumab as monotherapy and for nivolumab in combination with ipilimumab for the treatment of previously untreated adult patients with metastatic or unresectable Stage III or Stage IV melanoma. The Subcommittee noted that the application would also be considered by PTAC at its meeting to be held on 5-6 May 2016.

1.7 The Subcommittee noted that an application for ipilimumab monotherapy for the treatment of unresectable or metastatic Stage IIIc or IV melanoma had been considered by both PTAC and CaTSoP in 2012 and again by PTAC in 2014, and that both PTAC and CaTSoP had recommended the application be declined. The Subcommittee noted that, at its meeting in February 2016, PTAC reconsidered the application for ipilimumab monotherapy, including consideration of recently published long term follow-up data, and recommended that ipilimumab monotherapy be funded with a low priority for patients with previously treated unresectable stage IIIc and IV melanoma. The Subcommittee noted that the application for ipilimumab monotherapy was also being reconsidered by CaTSoP at its current meeting.

1.8 The Subcommittee noted that nivolumab is a monocolonal antibody in the class of treatments known as programmed death 1 protein (PD-1) inhibitors. The Subcommittee noted that PD-1 inhibitors bind to the PD-1 receptor expressed on the

surface of T-cells and block the interaction with tumour-expressed ligands PD-L1 and PD-L2 to inhibit T-cell activation and promote tumour immune escape.

1.9 The Subcommittee noted that ipilimumab is a monoclonal antibody that selectively binds to the cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) thereby enhancing T-cell activation and proliferation.

1.10 The Subcommittee noted the recommended dose of nivolumab as monotherapy is 3 mg/kg administered intravenously every 2 weeks until disease progression or unacceptable toxicity. The Subcommittee noted that the recommended dose for combination treatment is nivolumab 1 mg/kg with ipilimumab 3 mg/kg for the first four doses and the monotherapy dose thereafter.

Nivolumab monotherapy

1.11 The Subcommittee noted that the primary evidence for nivolumab as monotherapy for the treatment of advanced melanoma comes from CheckMate-066, a randomised, controlled, double-blind, phase III study of nivolumab compared to dacarbazine in 418 previously untreated patients with metastatic melanoma without a BRAF mutation (Robert et al NEJM 2015;372:320-30). The Subcommittee noted that patients 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/m^2 every 3 weeks and nivolumab-matched placebo every 2 weeks (n=208). Members noted that patients were stratified by PD-L1 status and metastasis stage and key exclusion criteria included active brain metastases, uveal melanoma, and serious autoimmune disease.

1.12 The Subcommittee noted that treatment continued until disease progression (according to RECIST version 1.1) or unacceptable toxicity (as assessed by investigator); with tumour response assessed at 9 weeks after randomisation, every 6 weeks in the first year and then every 12 weeks until disease progression or treatment discontinuation. Members noted that 54 patients in the nivolumab arm and 8 patients in the dacarbazine arm received treatment beyond disease progression.

1.13 The Subcommittee noted that immunologically driven criteria to assess response were developed during this trial, as the phenomenon of pseudo-progression had been recognised, and that treatment was allowed to continue provided there was clinical benefit for the patient. The Subcommittee noted that patients with progression at 3 months by RECIST were allowed to continue on therapy until a further confirmatory scan performed one month later.

1.14 The Subcommittee noted that in the original report of the study (Robert et al NEJM 2015;372:320-30) median overall survival (OS), the primary endpoint, was not reached in the nivolumab arm at the time of reporting and was 10.8 months (95% CI 9.3-12.1) in the dacarbazine arm. The Subcommittee noted the OS rate at one year was 72.9% (95% CI 65.5-78.9) in the nivolumab arm compared to 42.1% (95% CI 33.0-50.9) in the dacarbazine arm (HR 0.42, 99.79% CI 0.25-0.73, p<0.001). The median PFS was 5.1 months versus 2.2 months respectively (HR 0.43, 95% CI 0.34-0.56, p<0.001). The objective response rate (ORR) was 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 (OR 4.06, p<0.001).

1.15 The Subcommittee noted that treatment related adverse events (AE) of any grade were 74.3% in the nivolumab arm and 75.6% in the dacarbazine arm, however, AE of grade 3 or 4 occurred in only 11.7% and 17.6% nivolumab and dacarbazine groups

respectively. Members noted that in clinical practice drugs of this class seemed to be in general well tolerated, with a small number of significant immunologically mediated side effects.

1.16 The Subcommittee noted evidence from CheckMate-037 (Weber et al. Lancet Oncol 2015;16:375-384). This was a phase III randomised, controlled, open-label trial comparing nivolumab with chemotherapy (dacarbazine or paclitaxel/carboplatin) in patients with advanced melanoma with ipilimumab or ipilimumab and a BRAF inhibitor. Members noted that while CheckMate-066 was restricted to BRAF mutation negative patients Weber et al. reports response rates in BRAF V600 mutation-positive patients and BRAF wild-type patients to be equivalent.

1.17 The Subcommittee noted evidence from CheckMate-069 (Postow et al. N Engl J Med 2015;372:2006-1). This was a double-blind randomised phase II 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.

1.18 The Subcommittee noted that two year survival and safety results from CheckMate-066, the randomised, controlled, double-blind, phase III study of nivolumab compared to dacarbazine described earlier (9.11) were presented at Society for Melanoma Research (SMR) 2015 where it was reported that, at a median follow up of 18.5 months, the median OS was not reached in the nivolumab arm and 11.2 months in the dacarbazine group (Atkinson et al SMR 2015 poster presentation). Members noted that two year OS was 57.7% compared to 25.7% for the nivolumab and dacarbazine arms respectively.

1.19 The Subcommittee considered that the randomised placebo controlled trial design and use of dacarbazine as a comparator was appropriate in the New Zealand setting and provided a strong level of support for a survival benefit with nivolumab monotherapy for advanced melanoma patients over the current standard of care in New Zealand.

1.20 The Subcommittee considered that the CheckMate-066 trial was well designed in that it included a comparator treatment appropriate for the New Zealand setting, was placebo controlled, had limited crossover, and large patient numbers. The Subcommittee considered that the evidence for the use of nivolumab as monotherapy was of good strength and quality but noted its short duration of follow-up to date. The Subcommittee noted there was good quality evidence to support an overall survival benefit for nivolumab monotherapy over dacarbazine for patients with advanced melanoma. Members considered that patients with either BRAF positive or negative mutation status would likely benefit from treatment with nivolumab monotherapy; The Subcommittee considered that patients with very rapidly progressive disease would be unlikely to benefit from treatment with nivolumab monotherapy given the average length of time required for patients to receive benefit from treatment.

1.21 The Subcommittee considered that treatment with nivolumab should not be restricted to ipilimumab naïve or BRAF V600 mutation-positive patients.

1.22 The Subcommittee considered that, if more than one PD1 inhibitor was listed on the Pharmaceutical Schedule, treatment with nivolumab should be restricted to patients who had not had disease progression following treatment with another PD-1 inhibitor (and vice versa).

1.23 The Subcommittee noted that there were currently insufficient data to determine whether PDL1 expression could be used as a biomarker to target treatment to patients who would be more likely to receive clinically meaningful benefit. Members also noted that there was currently no widely available standard or reliable platform for testing PDL1 expression. The Subcommittee noted that at present there was no reliable biomarker to target treatment to patients who were more likely to achieve clinically meaningful benefit.

1.24 Members noted that from the currently available evidence, the recommended duration of treatment in a responding patient was unclear. Members also noted that it is unclear from the current evidence whether patients with a degree of concomitant autoimmune disease should receive treatment with drugs of this class, as they were excluded from the clinical trial population.

1.25 The Subcommittee **recommended** that nivolumab as monotherapy be funded with medium/high priority for the treatment of patients with metastatic or unresectable Stage IIIc or Stage IV melanoma noting this was based on the unmet health need of the patient population and strength of the evidence, but that the very high cost influenced the recommendation.

Nivolumab in combination with ipilimumab

1.26 The Subcommittee noted that the pivotal evidence for the use of nivolumab in combination with ipilimumab for the treatment of patients with advanced melanoma comes from CheckMate-067, a randomised, double-blind, phase 3 study comparing nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone in 945 previously untreated patients with unresectable stage III or IV melanoma (Larkin et al. N Engl J Med 2015; 373: 23-34).

1.27 The Subcommittee noted that patients were assigned 1:1:1 to receive treatment until progression or unacceptable toxicity with the following regimens:

- nivolumab 3 mg/kg every 2 weeks plus ipilimumab-matched placebo (n=316);
- nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four doses, followed by nivolumab 3 mg/kg every 2 weeks for cycle 3 and beyond (n=314);
- ipilimumab 3 mg/kg every 3 weeks for four doses plus nivolumab-matched placebo (n=315).

1.28 The Subcommittee noted that patients with both positive and negative BRAF V600 mutation were eligible for study participation and key exclusion criteria included ECOG performance-status score of 2 or greater, presence of active brain metastases, ocular melanoma, and autoimmune disease.

1.29 The Subcommittee noted that patients were assessed for tumour response according to RECIST version 1.1 at 12 weeks after randomisation, then every 6 weeks for 49 weeks, then every 12 weeks until progression of treatment discontinuation whichever occurred later. Members noted that patients could be treated after progression provided they had clinical benefit and an absence of substantial adverse events.

1.30 The Subcommittee noted that at database lock in February 2015 with a median follow-up ranging from 12.2 months to 12.5 months, 37.4%, 29.7% and 16.1% of patients in each arm respectively remained on study treatment. The Subcommittee

considered that this was indicative of early data with patients still actively being treated.

1.31 The Subcommittee noted that median PFS was 6.9 months (95% CI, 4.3 – 9.5) in the nivolumab monotherapy arm, 11.5 months (95% CI, 2.8-3.4) in the nivolumab plus ipilimumab arm, and 2.9 months (95% CI 2.98-3.4) in the ipilimumab monotherapy arm.

1.32 The Subcommittee noted that the incidence of treatment-related grade 3 or 4 adverse events was 16.3% in the nivolumab monotherapy group, 55% in the nivolumab plus ipilimumab group, and 27.3% in the ipilimumab monotherapy group and treatment-related adverse events that lead to discontinuation of the study drug occurred in 7.7%, 36.4% and 14.8% respectively.

1.33 The Subcommittee considered that the currently available data for combination treatment were too immature to draw any meaningful conclusion, and noted that there were a significant number of patients still receiving combination treatment indicating that reported data were from a time point within two months of enrolment of these patients.

1.34 The Subcommittee considered that the toxicity of the combination treatment was very high and appeared to be higher than observed in the ipilimumab monotherapy arm and at comparable stages of the nivolumab monotherapy trials.

General comments

1.35 The Subcommittee considered that there was a risk of increased DHB costs associated with the management of the adverse event profile of nivolumab treatment which could require substantive care and long term monitoring, although patient monitoring was unlikely to increase overall if nivolumab were funded.

1.36 The Subcommittee noted that currently most oncology agents were discontinued at disease progression. The Subcommittee considered that, while it was appropriate for nivolumab to be discontinued at disease progression, any access criteria for nivolumab should take into account the possibility of pseudo-progression, where a patient's disease may initially appear to have progressed but then show a response shortly afterwards. Members considered that if a CT scan showed progressive disease after the first 12 weeks (6 cycles) of treatment, this should be confirmed by a second CT scan 1 month later as per the trial protocol before mandating discontinuation of nivolumab. Members considered that in practice it was unlikely that scans would be able to be repeated at 4 weeks and that 6 weeks was currently the shortest possible time between scans in the New Zealand healthcare system (follow-up scan after 5 weeks with specialist visit 1 week later).

1.37 The Subcommittee considered that the number of patients who would be eligible for treatment with a PD-1 inhibitor, should one be funded, would be approximately 350 per year; however, the Subcommittee considered that it would be reasonable to expect at least double the number of patients in year one if a new treatment for advanced melanoma were to be funded.

1.38 The Subcommittee noted that the first year uptake of PD-1 inhibitors in Australia was lower than predicted; however, members considered this was unlikely to occur in New Zealand as other funded treatments were available in Australia and there were likely a higher proportion of patients participating in clinical trials in Australia.

1.39 The Subcommittee noted that the Pharmaceutical Benefits Advisory Committee in Australia recommended listing nivolumab as monotherapy treatment for patients with unresectable stage III or stage IV malignant melanoma limited to patients who have not been exposed to ipilimumab and if BRAF V600 mutation positive must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor), but did not recommend the combination of nivolumab and ipilimumab noting the clinical benefit of the combination was uncertain.