Cancer Treatments Subcommittee of PTAC
Meeting held 22 April 2016

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the Cancer Treatments Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatments Subcommittee discussions about an application or PHARMAC staff proposal that contains a recommendation are generally published.

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.

These Subcommittee minutes were reviewed by PTAC at its meeting 11 & 12 August 2016.

1 Matters Arising and Correspondence

Temozolomide

1.1 The Subcommittee noted correspondence from Dr Ben Lawrence, Medical Oncologist, in response to the March 2015 Cancer Treatments Subcommittee of PTAC (CaTSoP) minute relating to temozolomide for neuroendocrine tumours (NETs) which stated that the terms "well differentiated" and "low grade" were not interchangeable and **recommended** that the minute be amended.

1.2 The Subcommittee noted that there are three grades of NETs – NETG1, NETG2, and NEC – which are generally interpreted as low, intermediate and high grade respectively. The Subcommittee noted that NETG1 and NETG2 are always well differentiated and NEC can be either well or poorly differentiated.

1.3 The Subcommittee agreed this was an important distinction and **recommended** that the Subcommittee's previous recommendation be amended to "temozolomide be funded for patients with unresectable, well-differentiated NETs with medium priority."

1.4 The Subcommittee **recommended** that temozolomide for NETs be funded according to the following SA criteria:

> Initial application - (neuroendocrine tumours) only from a relevant specialist.
> Approvals valid for 9 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has been diagnosed with metastatic or unresectable well-differentiated neuroendocrine tumour*; and
> 2. Temozolomide is to be given in combination with capecitabine; and
> 3. Temozolomide is to be used in 28 day treatment cycles for a maximum of 5 days treatment per cycle at a maximum dose of 200 mg/m^2 per day; and
> 4. Temozolomide to be discontinued at disease progression.
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> Renewal application - (neuroendocrine tumours) only from a relevant specialist.
> Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of disease progression; and
> 2. The treatment remains appropriate and the patient is benefitting from treatment.
>
> Notes: Indication marked with a * is an Unapproved Indication.

$5HT_3$ receptor antagonist injections

1.5 The Subcommittee noted that the Analgesic Subcommittee recommended that advice be sought from CaTSoP regarding the $5HT_3$ receptor antagonists and in particular the clinical need for tropisetron injection for post operative nausea and vomiting.

1.6 The Subcommittee considered that most oncologists preferred short-acting $5HT_3$ receptor antagonists. Members considered that the choice of long-acting agent was a commercial decision and that switching patients from one $5HT_3$ receptor antagonist to another was unlikely to be problematic. Members further noted that

if only one long-acting $5HT_3$ receptor antagonist was registered for paediatric use then this would be the preferred agent.

Gonadotropin-releasing hormone (GnRH) analogues RFP update

1.7 The Subcommittee noted that the GnRH analogue Request for Proposals (RFP) would close on 21 April 2016 and that PHARMAC would update the Subcommittee prior to any decision being made.

2 Lenalidomide review

2.1 The Subcommittee reviewed the usage and expenditure of currently funded newer treatments for multiple myeloma (thalidomide, bortezomib and lenalidomide). The Subcommittee noted that current expenditure on lenalidomide is significantly higher than estimated prior to listing on 1 September 2014 and now represents 50% of the total cost of newer treatments for multiple myeloma, with bortezomib representing the other half.

2.2 The Subcommittee noted that Australia had similarly experienced a much higher level of lenalidomide use than expected.

Current access

2.1 The Subcommittee noted that lenalidomide is currently listed on the Pharmaceutical Schedule for the second and third-line treatment of relapsed/refractory multiple myeloma (MM) according to Special Authority criteria.

2.2 The Subcommittee noted that MM specific mortality is about 60% and that most patients who die from MM would receive multiple lines of treatment. Based on the number of patients with Special Authority approvals, the Subcommittee considered that the total number of patients accessing funded lenalidomide was broadly representative of the MM population levels and trends in MM diagnosis in New Zealand.

2.3 The Subcommittee considered that, of the approximately 350 patients in New Zealand currently diagnosed with MM, one third would be maintained on first or second-line treatment or not progress to third-line treatment for varying reasons, and two thirds of patients would progress to third-line treatment, many with lenolidomide. Members considered that an appropriate estimate of the number of new patients starting treatment with lenalidomide would be 17 patients per month currently. The Subcommittee noted this was consistent with the number of Special Authority applications being made each month.

2.4 The Subcommittee considered that Special Authority data indicated that the proportion of patients accessing lenalidomide in a second-line setting was in line with estimates of the incidence of peripheral neuropathy but there was a larger proportion of the total MM population accessing treatment in a third-line setting than expected.

2.5 The Subcommittee noted that, of the 237 patients with Special Authorities approved in the third-line setting, only 68% had previously been dispensed both thalidomide and bortezomib with the remaining patients being dispensed only one of these treatments. Therefore, up to 40% of patients with Special Authority approvals in the third-line setting appeared to effectively be accessing lenalidomide as a second-line treatment.

2.6 The Subcommittee considered that one of the reasons for this may be due to concerns about alkylating agent exposure and a desire to obtain early benefit from lenalidomide, which has greater efficacy when used earlier in the disease course. The Subcommittee considered that there had likely also been a change in clinical practice where thalidomide and bortezomib are administered in combination or in quick succession, without disease progression in between, which clinicians appear to be interpreting as two lines of treatment. Members considered that treatments administered sequentially, according to a plan, without disease progression in between, should be considered as a single line of treatment.

2.7 The Subcommittee considered that the difference in interpretation of what constitutes a line of treatment means that patients are receiving lenalidomide earlier in their disease course than expected and, therefore, their duration of treatment with lenalidomide will be longer than expected.

2.8 The Subcommittee noted that treatment in second-line settings is three times longer than for third-line settings. The Subcommittee noted that if 40% of patients received lenalidomide earlier than expected at second-line rather than third-line treatment, the average length of treatment would be 1.8 times longer than expected. The Subcommittee noted that the treatment duration for patients with Special Authority approvals for third-line lenalidomide are on average receiving twice the duration estimated prior to listing, i.e. 9-10 months rather than 4.5 months.

2.9 The Subcommittee noted that since lenalidomide was listed the number of patients receiving funded treatment has been increasing. However, the Subcommittee considered that this would plateau and members considered that a steady state had likely now been reached.

2.10 The Subcommittee **recommended** that the Special Authority criteria for lenalidomide for relapsed or refractory MM be amended as follows (additions in bold):

> LENALIDOMIDE – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (Relapsed/refractory disease) - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
> 2. Either:
> 2.1. Lenalidomide to be used as third line* treatment for multiple myeloma; or
> 2.2. Both:

2.2.1. Lenalidomide to be used as second line treatment for multiple myeloma, and
2.2.2. The patient has experienced severe (grade ≥3), dose limiting, peripheral neuropathy with either bortezomib or thalidomide that precludes further treatment with either of these treatments; and

3. Patient has received previous treatment with thalidomide; and

4. Lenalidomide to be administered at a maximum dose of 25 mg/day in combination with dexamethasone.

Renewal **(Relapsed/refractory disease)** - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. No evidence of disease progression, and
2. The treatment remains appropriate and patient is benefitting from treatment.

Notes: Indication marked with * is an Unapproved Indication (refer to Interpretations and Definitions). A line of treatment is considered to end upon progressive disease and comprise either: a) a known therapeutic chemotherapy regimen and supportive treatments or b) a transplant induction chemotherapy regimen, stem cell transplantation**, consolidation,** and supportive treatments. **Grade 3 peripheral neuropathy is defined as "interfering with daily activities".** Prescriptions must be written by a registered prescriber in the lenalidomide risk management programme operated by the supplier.

2.11 The Subcommittee considered that it would be useful to seek advice from the Neurology[1] Subcommittee of PTAC prior to any changes being made to the Special Authority criteria for lenalidomide.

Widening of access

2.12 The Subcommittee noted that PHARMAC had received a number of NPPA applications for first-line lenalidomide in patients with MM and pre-existing peripheral neuropathy, where the applicants considered that treatment with thalidomide and bortezomib was inappropriate due to the presence pre-existing neuropathy.

2.13 The Subcommittee noted that, internationally, lenalidomide is widely used as a first-line treatment as it is well tolerated and associated with a lower risk of peripheral neuropathy compared with thalidomide (2%-3% versus 40% risk respectively).

2.14 The Subcommittee noted that first-line treatment with lenalidomide had not previously been considered by either CaTSoP or PTAC.

2.15 The Subcommittee considered that funded access to first-line treatment with lenalidomide for all patients with any pre-existing neuropathy would be a significant financial investment.

2.16 The Subcommittee considered that lenalidomide would be a clinically appropriate first-line option for patients with ≥ grade 3 pre-existing peripheral neuropathy. Members considered that the cause of a patient's pre-existing neuropathy was not relevant in determining whether bortezomib and thalidomide were

[1] Typographical error – CaTSoP confirmed in its September 2016 meeting this was incorrectly stated as the Haematology Subcommittee

contraindicated. The Subcommittee considered there would be a low financial risk in funding lenalidomide for this indication as there would likely be around two patients every five years in New Zealand with treatment naïve MM and ≥ grade 3 pre-existing peripheral neuropathy.

2.17 The Subcommittee **recommended** that lenalidomide in combination with dexamethasone be funded for the first-line treatment of patients with grade 3 or greater pre-existing neuropathy with a medium/high priority subject to the following Special Authority criteria:

> LENALIDOMIDE – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (treatment naive disease) - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has treatment naive multiple myeloma with progressive disease; and
> 2. Patient has severe (grade ≥3) pre-existing peripheral neuropathy; and
> 3. Lenalidomide to be administered at a maximum dose of 25 mg/day in combination with dexamethasone.
>
> Renewal (treatment naïve disease) - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression, and
> 2. The treatment remains appropriate and patient is benefitting from treatment.

3 Pomalidomide for multiple myeloma

Application

3.1 The Subcommittee considered an application from Celgene Pty Ltd for the funding of pomalidomide (Pomalyst) in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma in patients who have received at least two prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Recommendation

3.2 The Subcommittee **recommended** that pomalidomide in combination with dexamethasone be funded with a low priority for the treatment of relapsed or refractory multiple myeloma in patients who have received at least two prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy, subject to the following Special Authority criteria:

> POMALIDOMIDE – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (relapsed/refractory disease) - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has relapsed or refractory multiple myeloma with progressive disease; and

2. Either:
    2.1. Both:
        2.1.1 Pomalidomide is to be used as fourth-line treatment for multiple myeloma; and
        2.1.2 Patient has received previous treatment with lenalidomide, bortezomib, and thalidomide; and
    2.2 All of the following:
        2.2.1 Pomalidomide is to be used as third-line treatment for multiple myeloma; and
        2.2.2. Patient has received previous treatment with lenalidomide, and
        2.2.3. The patient has experienced severe (grade ≥3), dose limiting, peripheral neuropathy with either bortezomib or thalidomide that precludes further treatment with either of these treatments; and
3. Pomalidomide to be administered at a maximum dose of 4 mg/day for 21 days per 28 day cycle in combination with dexamethasone.

Renewal (relapsed/refractory disease) - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of disease progression, and
2. The treatment remains appropriate and patient is benefitting from treatment.

Notes: A line of treatment is considered to end upon progressive disease and comprise either: a) a known therapeutic chemotherapy regimen and supportive treatments or b) a transplant induction chemotherapy regimen, stem cell transplantation, consolidation, and supportive treatments. Grade 3 peripheral neuropathy is defined as “interfering with daily activities”. Prescriptions must be written by a registered prescriber in the pomalidomide risk management programme operated by the supplier.

3.3 The Subcommittee has taken into account, where applicable, PHARMAC's relevant decision-making framework in relation to this recommendation.

Discussion

3.4 The Subcommittee noted that multiple myeloma (MM) is a haematological malignancy that predominantly affects elderly patients, is currently not considered curable rather treatment goals in patients with MM are to delay disease progression and extend and/or improve quality of life.

3.5 The Subcommittee noted that the current treatment paradigm for MM in New Zealand was first line treatment with cyclophosphamide, bortezomib and dexamethasone, with or without SCT, and consolidation with a thalidomide-containing regimen. Generally thalidomide is used as second-line treatment, in combination with dexamethasone plus or minus cyclophosphamide, and lenalidomide is funded as third-line treatment.

3.6 The Subcommittee considered that patients with relapsed or refractory MM who had disease progression on two or more lines of treatment had a high health need as last-line treatments, such as high-dose dexamethasone, were palliative.

3.7 The Subcommittee noted that pomalidomide is part of a class of immunomodulatory drugs (IMiDs) that includes thalidomide and its analogues, lenalidomide.

3.8 The Subcommittee noted that the application for pomalidomide had previously been considered by PTAC at its February 2016 meeting where the Committee recommended funding with a low priority for the treatment of patients with relapsed and refractory MM who have received at least two prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on last therapy. Members noted that PTAC further recommended that the application be referred by the Cancer Treatments Subcommittee for consideration.

3.9 The Subcommittee noted the primary study for the use of pomalidomide in the treatment of relapsed/refractory MM is the MM-003 study (primary citation: San Miguel et al. Lancet Oncol 2013;14:1055-66) a phase III multi-centre, randomized, open label study of 455 patients with relapsed and refractory MM, who had failed at least 2 previous treatments including bortezomib and lenalidomide, alone or in combination, and had progressive disease since last treatment or intolerance of bortezomib.

3.10 The Subcommittee noted that exclusion criteria included: previous treatment with pomalidomide; hypersensitivity to thalidomide, lenalidomide or dexamethasone; resistance to high dose dexamethasone (HDD); or grade 2 or more peripheral neuropathy.

3.11 The Subcommittee noted patients were randomised to receive either 28 day cycle pomalidomide, at a dose of 4 mg per day on days 1-21, plus low-dose dexamethasone (LDD) at a dose of 40 mg on days 1, 8, 15 and 22, (n=302) compared with high-dose dexamethasone (HDD) alone at a dose of 40 mg per day on days 1-4, 9-12, and 17-20 (n=153) until disease progression or unacceptable toxicity.

3.12 The Subcommittee noted that patients with progressive disease on HDD could crossover to receive pomalidomide at the same dose but without dexamethasone in the companion trial MM-003C and, at the time of final PFS analysis, patients in the HDD arm who had not progressed could crossover to receive pomalidomide with or without dexamethasone.

3.13 The Subcommittee noted that, after a median follow up of 10.0 months (IQR 7.2-3.2) median progression free survival (PFS), the primary endpoint, was 4.0 months (95% CI 3.6-4.7) in the pomalidomide/LDD arm compared with 1.9 months (95% CI 1.9-2.2) in the HDD arm (HR 0.48, 95% CI 0.39-0.60, p<0.0001). The Subcommittee noted that median OS was 12.7 months (95% CI 10.4-15.5) compared with 8.1 months (95% CI 6.9-10.8) in the pomalidomide/LDD and HDD arms respectively (HR 0.74, 0.56-0.97, p=0.0285).

3.14 The Subcommittee noted that the overall response rate was 31% v 10% and in patients with at least a partial response, median response duration was 7.0 months (95% CI 5.8-9.0) compared with 6.0 months (95% CI 1.4-8.5) in the pomalidomide/LDD and HDD arms respectively (HR 0.52, 95% 0.25-1.05, p=0.0631).

3.15 The Subcommittee noted that grade 3-4 haematological adverse events were reported in 48% of patients in the pomalidomide/LDD arm compared with 16% in

the HDD arm and treatment-related adverse events leading to death were reported in 4% of patients in the pomalidomide/LDD arm compared with 5% of patients in the HDD arm.

3.16 The Subcommittee noted that pomalidomide has a significant side effect profile Members considered the primary concern to be haematological toxicity, which was often pronounced in late-stage MM, with 43% of patients in the pomalidomide/LDD arm requiring granulocyte colony stimulating factor (G-CSF) compared with only 10% requiring G-CSF in the HDD arm.

3.17 The Subcommittee considered that the evidence for use of pomalidomide in a fourth-line setting was of good strength and quality. The Subcommittee noted that nearly all patients in MM-003 had received three previous lines of treatment and all had been previously treated with both bortezomib and lenalidomide and was therefore a comparable population to fourth-line MM patients in New Zealand.

3.18 The Subcommittee considered that response to pomalidomide appeared to be similar in all subgroups providing small PFS and OS gains but at the expense of manageable toxicity requiring high-level care.

3.19 The Subcommittee noted that pomalidomide was administered orally and at the same dose rate as lenalidomide and had similar myelosuppressive effects, [redacted]

3.20 The Subcommittee considered that if pomalidomide were to be funded it is likely patients would move to new treatments earlier, as has been observed since lenalidomide was funded; therefore while the treatment duration with lenalidomide would reduce, this would result in a longer treatment duration with pomalidomide [redacted]

3.21 The Subcommittee noted that there is a large number of new agents, including new generation of current classes and those with entirely different mechanisms of action such as antibodies targeted against plasma cell antigens and immune checkpoint inhibitors, which are currently in development for the treatment of MM both as monotherapy and as combination therapies. Members noted that many had been approved for use internationally in the last year and considered that these treatments were likely to enter the New Zealand market in the near future.

4 Dabrafenib/trametinib for BRAF v600 metastatic melanoma

Application

4.1 The Subcommittee considered an application from Novartis Pharmaceuticals for the funding of dabrafenib (Tafinlar) and trametinib (Mekinist) for use in combination for the treatment of BRAF V600 mutation-positive unresectable (Stage III) or metastatic (Stage IV) malignant melanoma.

Recommendation

4.2 The Subcommittee **recommended** that dabrafenib and trametinib for use in combination for the treatment of BRAF V600 unresectable (Stage III) or metastatic (Stage IV) malignant melanoma be funded with a high priority in the absence of other funded treatments for melanoma due to the high health need of the patient population, subject to the following Special Authority criteria:

> DABRAFENIB – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has BRAF V600 mutation positive unresectable (Stage III) or metastatic (Stage IV) melanoma; and
> 2. Patient's disease has not progressed following previous treatment with a BRAF or MEK inhibitor; and
> 3. Dabrafenib to be administered at a maximum dose of 300 mg per day in combination with trametinib.
>
> Renewal (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression, and
> 2. The treatment remains appropriate and patient is benefitting from treatment.
>
> TRAMETINIB – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has BRAF V600 mutation positive unresectable (Stage III) or metastatic (Stage IV) melanoma; and
> 2. Patient's disease has not progressed following previous treatment with a BRAF or MEK inhibitor; and
> 3. Trametinib to be administered at a maximum dose of 2 mg per day in combination with dabrafenib.
>
> Renewal (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression, and
> 2. The treatment remains appropriate and patient is benefitting from treatment.

4.3 The Subcommittee noted the priority rating for dabrafenib/trametinib was based on a lack of effective funded options for the treatment of advanced melanoma and considered that should another class of treatment for melanoma be funded the priority of dabrafenib/trametinib would be lower.

4.4 The Subcommittee has taken into account, where applicable, PHARMAC's relevant decision-making framework in relation to this recommendation.

Discussion

4.5 The Subcommittee noted that New Zealand has the highest incidence of melanoma globally and considered that there was a high unmet health need for effective treatments for patients with unresectable or metastatic (advanced)

melanoma. The Subcommittee noted that the age-standardised rate of melanoma is 7-8 times higher in Māori compared with non-Māori.

4.6 The Subcommittee noted that the lifespan for advanced melanoma patients is typically measured in months and overall survival is poor for patients with advanced disease irrespective of mutational status with 20% 5-year survival rates.

4.7 The Subcommittee considered that internationally patients had access to a number of newer treatments for melanoma but that funded treatment options for melanoma patients in New Zealand are currently limited comprising solely of surgery, radiotherapy and dacarbazine, which has limited efficacy and therefore low uptake.

4.8 The Subcommittee noted that dabrafenib is an oral selective inhibitor of mutated forms of BRAF and tramatenib is an oral mitogen-activated protein/extracellular signal-regulated kinase (MEK) inhibitor. The Subcommittee noted that the combination dabrafenib/trametinib was indicated for advanced melanoma patients with BRAF V600 mutation positive disease. Members noted that BRAF mutation testing is routinely available and undertaken in New Zealand; however, methodologies varied between centres and the various tests had differing costs and limitations.

4.9 The Subcommittee noted that an application to fund dabrafenib as monotherapy for unresectable or metastatic BRAF V600 mutation positive melanoma has previously been considered by PTAC in 2014 and it was recommended the application be declined.

4.10 The Subcommittee noted that PTAC had considered the funding of dabrafenib in combination with trametinib for BRAF V600 mutation positive advanced melanoma at its November 2015 meeting. The Subcommittee noted that PTAC had recommended the application be declined noting the associated toxicity and that the magnitude and duration of benefit was unclear and further recommended that the application be referred by the Cancer Treatments Subcommittee for consideration.

4.11 The Subcommittee reviewed evidence for the use of dabrafenib/trametinib from the COMBI-D, BRF113220, COMBI-V, and BREAK-3 trials.

COMBI-D

4.12 The Subcommittee considered that the primary evidence for combination treatment of dabrafenib and trametinib came from the COMBI-D study: a phase III, randomised, double-blind study comparing combination dabrafenib and trametinib to dabrafenib and placebo in previously untreated patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma (Long et al. N Engl J Med 2014; 371: 1877-88. Long et al. Lancet 2015; 386: 444-51 and Schadendorf et al. European Journal of Cancer 2015; 51: 833- 40). Members noted that 423 patients were randomly assigned (1:1) to receive dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) (n= 211) or dabrafenib (150 mg twice daily) and placebo (n=212) with

treatment continued until disease progression, death, or withdrawal from the study. Members noted that inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and therefore patients with poorer performance status were not eligible.

4.13 The Subcommittee noted the results of COMBI-D reported in Long et al. Lancet 2015 reported median overall survival (OS) was 25.1 months (95% CI 19.2 - not reached) in the dabrafenib / trametinib arm versus 18.7 months in the dabrafenib only arm (HR 0.71, 95% CI 0.55 - 0.92; p=0.0107). The Subcommittee noted that investigator assessed median progression free survival (PFS), the primary endpoint of the study, was 11.0 months (95% CI 8.0-13.9) in the dabrafenib / trametinib arm versus 8.8 months (95% CI 5.9-9.3) in the dabrafenib only arm (HR 0·67, 95% CI 0·53-0·84; p=0·0004). Members noted that treatment-related adverse events occurred in 87% of patients in the dabrafenib / trametinib group and 90% of patients in the dabrafenib only group.

BRF113220

4.14 The Subcommittee considered supporting evidence from the BRF113220 trial, a phase II, open label but assessor blinded, randomised controlled study that compared combination dabrafenib (150 mg) and trametinib (1 or 2 mg) (n=162) with dabrafenib (150 mg) monotherapy (n=85) in patients with metastatic melanoma and BRAF V600 mutations (Flaherty et al. NEJM 2012;367;1694-703). The Subcommittee noted that after a median follow up of 14.1 months median PFS was 9.4 months in the combination group compared with 5.8 months in the monotherapy group (HR 0.39; 95% CI 0.25 to 0.62; p<0.001) and overall response rate (ORR) with combination therapy was 76% compared with 54% with monotherapy (p=0.03). Members considered the results of this study were confounded by crossover as patients who had disease progression while receiving monotherapy were permitted to cross over to receive combination treatment.

COMBI-V

4.15 The Subcommittee reviewed evidence from COMBI-V, an open-label phase III trial in which 704 previously untreated patients with metastatic melanoma with a BRAF V600 mutation were randomly assigned to receive either combination dabrafenib (150 mg twice daily) and trametinib (2 mg daily) or vemurafenib (960 mg twice daily) (Robert et al. NEJM 2015;372:30-9). The Subcommittee noted that at twelve months OS, the primary endpoint of the study, was 72% in the combination group and 65% in the vemurafenib group (HR 0.69; 95% CI, 0.53 to 0.89; p=0.005) and median PFS was 11.4 months in the combination group compared with 7.3 months in the vemurafenib group (HR, 0.56; 95% CI, 0.46 to 0.69; p<0.001). Members noted that the current 1 year survival rate in New Zealand was 50%.

BREAK-3

4.16 The Subcommittee reviewed evidence from BREAK-3: a phase III, open-label, randomized study comparing oral dabrafenib with intravenous dacarbazine in previously untreated patients with BRAF V600E mutation positive advanced

(stage III) or metastatic (stage IV) melanoma. during consideration of the application for dabrafenib monotherapy in November 2014 (Hauschild et al. Lancet. 2012;380:358-65, Latimer et al. J Clin Onc 2013;31; 9044, and Hauschild et al. unpublished abstract 5785: European Society of Medical Oncology (ESMO) conference 2014).

4.17 The Subcommittee noted that results from BREAK-3 indicated that median PFS as assessed by investigator, the primary endpoint of the study, was improved in the dabrafenib group (5.1 months compared with 2.7 months for the dacarbazine group (HR 0.30, 95% CI 0.18 - 0.51; p<0.0001)) and after a median follow-up of 16.9 months, median OS in the dabrafenib arm was 20.0 months compared with 15.6 months in the darcarbazine arm (HR=0.77) plus crossover 62% received treatment with another agent.

4.18 The Subcommittee noted that a formal indirect treatment comparison of combination dabrafenib/trametinib and dacarbazine, the currently funded treatment in New Zealand, had been supplied by the applicant using the results from COMBI-D and BREAK-3. The Subcommittee considered that the indirect comparison undertaken by the supplier was appropriate; however, members considered that it was difficult to determine the magnitude or duration of benefit New Zealand patients may achieve from treatment with dabrafenib/trametinib based on an indirect comparison.

4.19 The Subcommittee considered that the strength and quality of the evidence was good and that the absence of an appropriate comparator arm for the New Zealand setting should not be interpreted as criticism of the study design given that New Zealand did not currently fund some treatments that are considered international standard care for advanced melanoma.

General comments

4.20 The Subcommittee noted that it did not agree with parts of the November 2015 PTAC meeting minute regarding the application for dabrafenib and trametinib, in particular regarding the toxicity of dabrafenib/trametinib. Members noted that the figures reported from the Medsafe datasheet regarding visual disturbances and cardiac evaluation (paragraph 7.17) were considered to be high compared with what was observed in clinical practice. Members also noted that there appeared to be a discrepancy in the reporting of haemorrhagic events in the Medsafe datasheet (as described in paragraph 7.18 of the PTAC minute) and that anecdotal evidence suggested haemorrhagic adverse events were not seen in clinical practice. The Subcommittee considered dabrafenib/trametinib to be very tolerable with manageable toxicity.

4.21 The Subcommittee considered that there was a place for BRAF and MEK inhibitors in the treatment paradigm for advanced melanoma and that they would likely be used first-line for patients with BRAF mutation positive disease, primarily to gain disease control due to the short time to disease response in responding patients, prior to maintenance or second-line treatment with PD1 inhibitors.

4.22 The Subcommittee considered that, due to the small subgroup of advanced melanoma patients who would benefit from this treatment and the very high

proposed price currently being sought for the combination treatment, that other new melanoma treatments indicated for the wider advanced melanoma patient group, such as a PD1 inhibitor, could provide a better investment for the health budget.

5 Nivolumab for advanced melanoma

Application

5.1 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

5.2 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.

5.3 The Subcommittee has taken into account, where applicable, PHARMAC's relevant decision-making framework as appropriate in relation to this recommendation.

5.4 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

5.5 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.

5.6 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.

5.7 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.

5.8 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.

5.9 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.

5.10 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

5.11 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 with 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.

5.12 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.

5.13 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.

5.14 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 with 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 with 13.9% (95% CI 9.5-19.4) in the dacarbazine arm (OR 4.06, p<0.001).

5.15 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.

5.16 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 previously treated 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.

5.17 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 1 mg/kg or placebo every three weeks for four doses followed by nivolumab 3mg/kg or placebo every 2 weeks until disease progression or unacceptable toxicity.

5.18 The Subcommittee noted that two year survival and safety results from CheckMate-066, the randomised, controlled, double-blind, phase III study of nivolumab compared with 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 with 25.7% for the nivolumab and dacarbazine arms respectively.

5.19 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.

5.20 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.

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

5.22 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).

5.23 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.

5.24 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.

5.25 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

5.26 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).

5.27 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).

5.28 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.

5.29 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.

5.30 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.

5.31 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.

5.32 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.

5.33 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.

5.34 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

5.35 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.

5.36 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).

5.37 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.

5.38 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.

5.39 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.

This minute, Nivolumab for Advanced Melanoma, was signed by the Chair on 5 May 2016 and reviewed by PTAC during its 5-6 May 2016 meeting.

6 Iplimumab for previously treated and unresectable stage IIIC or IV melanoma

Application

6.1 The Subcommittee considered the application from Bristol Myers Squibb (NZ) Limited, for the funding of ipilimumab (Yervoy) for the treatment of patients with previously treated unresectable stage IIIc or IV melanoma. This included the recently published long term follow up survival data from the pivotal randomised study.

Recommendation

6.2 The Subcommittee **recommended** that ipilimumab as monotherapy be funded with a medium priority for the treatment of patients with unresectable stage IIIc or IV melanoma in the absence of other funded treatments for melanoma due to the high health need of the patient population but noting the toxicity profile and high cost of treatment, subject to the following Special Authority criteria:

> IPILIMUMAB – PCT only
> Special Authority for Subsidy
> Initial application (advanced melanoma) - only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has unresectable (Stage III) or metastatic (Stage IV) melanoma; and
> 2. Patient has not received previous treatment with ipilimumab; and
> 3. Patient as a life expectancy of greater than 3 months; and
> 4. Ipilimumab to be administered as monotherapy at a maximum dose of 3 mg/kg every 3 weeks for a maximum of four doses.

6.3 The Subcommittee has taken into account, where applicable, PHARMAC's relevant decision-making framework in relation to this recommendation.

Discussion

6.4 The Subcommittee noted that the funding of ipilimumab monotherapy had previously been considered by PTAC at its February 2014 and August 2012 meetings where it recommended that the application be declined because the evidence for long term overall survival was of poor quality and there remained uncertainty of the magnitude of benefit from ipilimumab. The Subcommittee noted that it had considered the application at its October 2012 meeting where it recommended the application be declined because the evidence for any long term benefit was weak.

6.5 The Subcommittee noted that the key evidence previously considered for ipilimumab monotherapy in the treatment of advanced melanoma was from two randomised controlled phase III clinical trials, one for first-line treatment (Robert et al. 2011 NEJM 2011; 364:2517-26) and the other for second-line treatment (Hodi et al. 2010 NEJM 2010;363:711-23).

6.6 The Subcommittee noted that PTAC had re-considered the application at its February 2016 meeting after publication of the long-term overall survival (OS) evidence by Maio et al. (JCO 2015;33:1191-9) which reported the five year survival rates for treatment naïve patients with advanced melanoma who received ipilimumab in the phase III randomised trial reported by Robert et al. 2011.

6.7 The Subcommittee noted that median OS was 11.2 months (95% confidence interval (CI) 9.5-13.8) in the ipilimumab-dacarbazine arm compared with 9.1 months (95% CI, 7.8-10.5) in the placebo-dacarbazine arm and at a minimum follow up of 5 years, 18.2% of patients in the ipilimumab-dacarbazine treatment arm were still alive at 5 years compared with 8.8% of patients in the placebo-dacarbazine arm.

6.8 The Subcommittee reviewed evidence from a pooled analysis of long-term follow up of ipilimumab pre-treated advanced melanoma patients from the phase II and III studies published as Schadendorf et al. (JCO 2015; 33;1-7). The Subcommittee noted that this evidence was considered by PTAC at its February 2014 meeting prior to publication.

6.9 The Subcommittee considered that ipilimumab treatment was still associated with a significant toxicity profile, which was a contributing factor in the initial decline recommendation by both PTAC and the Subcommittee; however, the long-term survival data provided good strength and quality evidence to support the magnitude and durability of a survival benefit over dacarbazine for patients with advanced melanoma.

6.10 The Subcommittee noted that the evidence indicated that there was a delay of 2-3 months before patients demonstrated a response from treatment with ipilimumab monotherapy and, therefore, the Subcommittee considered that patients with a life expectancy of greater than 3 months would benefit most from treatment.

6.11 The Subcommittee considered that it was possible patients with advanced melanoma would receive benefit from rechallenge with ipilimumab; however, the evidence presented did not support ipilimumab retreatment.

6.12 The Subcommittee noted that a funding application for ipilimumab in combination with nivolumab for the treatment of previously untreated adult patients with metastatic or unresectable Stage III or Stage IV melanoma was also being considered at this meeting.

6.13 The Subcommittee considered that ipilimumab as monotherapy should be funded with medium priority for patients with unresectable stage IIIc or IV melanoma in the absence of other funded treatments for melanoma due to the high health need of the patient population but noting the low cost effectiveness with proposed pricing and high toxicity profile.

7 Melanoma and PD-1 inhibitor discussion

Application

7.1 The Subcommittee considered a supplementary paper from PHARMAC staff regarding the currently available evidence for PD-1 inhibitors for the treatment of melanoma and other cancers, the possibility of a competitive process in this market, and proposed Special Authority criteria for PD-1 inhibitors for the treatment of advanced melanoma.

Discussion

7.2 The Subcommittee noted that the PD-1 inhibitors at the most advanced stages of clinical trials are pembrolizumab (Keytruda, Merck Sharpe & Dohme) and nivolumab (Opdivo, Bristol-Myers Squibb), both of which have been brought to market internationally.

7.3 The Subcommittee noted there are a large number of ongoing clinical trials investigating a number of PD-1 inhibitors, as monotherapy and in combination therapies, for the treatment of a large variety of different cancer types.

Pembrolizumab

7.4 The Subcommittee noted that the application from Merck Sharpe & Dohme (MSD) for the funding of pembrolizumab (Keytruda) for the treatment of patients with metastatic or unresectable melanoma stage III or IV had been considered by PTAC at its November 2015 meeting and by the Cancer Treatments Subcommittee at their meeting in September 2015. The Subcommittee noted that both PTAC and the Subcommittee had recommended funding pembrolizumab with low priority.

7.5 The Subcommittee noted that the key evidence for the use of pembrolizumab in the treatment of advanced melanoma was from the following studies:

- KEYNOTE-001 (Hamid et al. N Engl J Med 2013;369:134-44) an open label multicenter, phase 1 dose escalation study in patients with locally advanced or metastatic melanoma or non-small cell lung cancer.

- KEYNOTE-002 (Ribas et al. Lancet Oncol 2015;16:908-18) a randomised phase II study comparing two dosing regimens of pembrolizumab (2mg/kg or 10mg/kg) given every three weeks with investigator-choice chemotherapy in patients with advanced melanoma refractory to prior treatment with ipilimumab and, if BRAF V600 mutant-positive, refractory to previous treatment with a BRAF or MEK inhibitor or both.

- KEYNOTE-006 (Robert et al. N Engl J Med 2015;372:2521-32) a randomised, controlled, phase III study of pembrolizumab given at 10mg/kg every 2 weeks or every 3 weeks.

Nivolumab

7.6 The Subcommittee noted that two funding applications from Bristol-Myers Squibb for nivolumab (Opdivo) were being considered at this meeting - as monotherapy and in combination with ipilimumab (Yervoy) for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma and for the treatment of locally advanced or metastatic squamous or non-squamous non-small cell lung cancer. The Subcommittee noted that these funding applications for nivolumab had not yet been considered by PTAC.

7.7 The Subcommittee noted that the key evidence for the use of nivolumab as monotherapy for the treatment of advanced melanoma comes from CHECKMATE-066 - a randomised, controlled, double-blind, phase III study of nivolumab compared with dacarbazine in previously untreated patients who had metastatic melanoma without a BRAF mutation (Robert et al. N Engl J Med 2015;372:320-30).

7.8 The Subcommittee noted that the key evidence for the use of nivolumab in combination with ipilimumab comes from three Phase III trials:

- 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.

- CHECKMATE-067 (Larkin et al. N Engl J Med 2015; 373: 23-34) is a randomised, double-blind, phase III study comparing nivolumab alone, nivolumab plus iplilimumab, or ipilimumab alone in 945 previously untreated patients with unresectable stage III or IV melanoma.

- 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 1 mg/kg or placebo every three weeks for four doses followed by nivolumab 3mg/kg or placebo every two weeks until disease progression or unacceptable toxicity.

General comments

7.9 The Subcommittee considered that, based on the currently available evidence for PD-1 inhibitors for the treatment of advanced melanoma, acknowledging that much of the evidence was immature, the evidence for the use of nivolumab as monotherapy (CHECKMATE-066) was of the highest strength and quality in that it included a comparator treatment appropriate for the New Zealand setting, was placebo controlled, had limited crossover, and large patient numbers.

7.10 The Subcommittee noted that based on the currently available evidence, noting the difference in trial design and absence of head to head comparative data, that pembrolizumab and nivolumab appeared to be mechanistically similar and the Subcommittee considered that the two treatments would provide the same or similar therapeutic effect in the treatment of advanced melanoma to the extent that it would be reasonable to run a competitive process that would result in only one PD-1 inhibitor being funded.

7.11 The Subcommittee noted that the funding application for each treatment was assessed individually and recommended for funding (or decline) based on the evidence available for each pharmaceutical. However, the Subcommittee considered that of the current classes of treatment for advanced melanoma that

funding for a PD-1 inhibitor would be its highest priority based on its mechanism of action, level of efficacy for all advanced melanoma patients, and tolerability effect profile.

7.12 The Subcommittee noted that if a PD-1 inhibitor was funded, the order of priority for funding for the remaining unfunded melanoma treatments would be a BRAF inhibitor or BRAF/MEK inhibitor combination treatment followed by ipilimumab as monotherapy primarily due to the toxicity profile of ipilimumab.

7.13 The Subcommittee considered that in the absence of a funded PD-1 inhibitor, funding of ipilimumab monotherapy would be a higher priority than a BRAF inhibitor or BRAF/MEK inhibitor because ipilimumab could be used in all patients with advanced melanoma whereas only the BRAF mutation positive subgroup of the advanced melanoma population would benefit from a BRAF targeted treatment.

PD-1 inhibitor access criteria

7.14 The Subcommittee considered a set of Special Authority criteria for PD-1 inhibitors for advanced melanoma proposed by PHARMAC staff.

7.15 The Subcommittee noted that the proposed Special Authority criteria for PD-1 inhibitors for advanced melanoma specified a 3 month (13 week) approval period. Members considered that given delays in commencing treatment, such as the time for scan results to be obtained, a 4 month Special Authority period would be more appropriate and workable.

7.16 The Subcommittee considered that, due to the delayed response to treatment, generally 8-16 weeks, patients with rapidly progressive disease were unlikely to benefit from treatment with PD-1 inhibitors and that funding should be restricted to patients with Eastern Cooperative Oncology Group (ECOG) performance scores of ≤ 2.

7.17 The Subcommittee considered that patients should receive treatment for brain metastases prior to commencing PD1 inhibitor therapy and that brain imaging prior to commencing would ensure patients could receive uninterrupted PD-1 inhibitor therapy.

7.18 The Subcommittee considered that it may be appropriate to limit the duration of treatment to 96 weeks or 2 years as this was the maximum treatment duration currently reported in the literature; however, members noted that clinical trial protocols were for treatment until disease progression and studies were ongoing. Members considered that it may be appropriate for patients who have had a good response to stop PD-1 inhibitor treatment for reasons other than disease progression. Members considered that it would be appropriate for the access criteria to allow patients who have had a period of time off treatment, and no disease progression, to recommence treatment. Members considered it may be appropriate to set up a registration trial to determine whether a fixed duration of treatment is appropriate.

7.19 The Subcommittee considered that there was a lack of evidence to support retreatment with PD-1 inhibitors following relapse.

7.20 The Subcommittee noted that currently most oncology treatments are discontinued at disease progression as measured by WHO or RECIST criteria; however, 3%-10% of advanced melanoma patients treated with immune stimulating agents have different patterns of response and may develop progression of disease as measured by conventional WHO or RECIST criteria before demonstrating clinical objective responses and/or stable disease. Members noted this phenomenon is referred to as 'pseudoprogression' an initial increase in tumour lesion size with subsequent decreased tumour burden.

7.21 The Subcommittee noted that under the proposed Special Authority criteria patients with pseudoprogression would not be eligible for ongoing funding. The Subcommittee considered that the access criteria for PD-1 inhibitors should allow for patients with pseudoprogression to receive an additional 4-6 weeks of treatment until re-assessment and confirmation of response could be determined at the following assessment. Members considered it was difficult to clearly clinically define pseudoprogression in such a way that a one-off renewal would be limited to patients with pseudoprogression only, and not all patients who showed disease progression. Members considered that without a clear definition this may mean that all patients would receive an additional 4-6 weeks regardless of whether their disease had progressed or not, which would represent a significant fiscal risk.

7.22 The Subcommittee considered that it may not be appropriate for patients who are responding to treatment long-term to require three-monthly scans as specified by the proposed access criteria.

7.23 The Subcommittee noted that while RECIST criteria are considered to be the standard measurement protocol for measuring solid tumour response to cancer treatments, in recent years alternative Immune Related Response Criteria (irRC), have been developed for measuring the response to immune-oncology treatments. Members considered that it would be appropriate for response to PD-1 inhibitor treatment to be measured using irRC rather than RECIST; however, members noted that the familiarity of NZ clinicians with use of irRC was uncertain.

7.24 The Subcommittee requested that, as there were a number of outstanding issues related to the proposed access criteria for PD-1 inhibitor treatments, that this should be brought back to them for further considered at their next meeting.

8 Nivolumab for non-small cell lung cancer

Application

8.1 The Subcommittee considered an application from Bristol-Myers Squibb (NZ) Ltd (BMS) for the funding of nivolumab (Opdivo) for the treatment of locally advanced or metastatic squamous and nonsquamous non-small cell lung cancer (NSCLC) for patients who have progressed on or after prior platinum-based chemotherapy.

Recommendation

8.2 The Subcommittee **recommended** that nivolumab as monotherapy be funded with a medium/low priority for the treatment of patients with locally advanced or metastatic squamous NSCLC that has progressed on or after prior platinum-based chemotherapy, subject to the following Special Authority criteria:

Nivolumab- PCT only - Specialist
Special Authority for Subsidy
Initial Application - only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1 Patient has locally advanced or metastatic squamous non-small cell lung cancer; and
2 Patients has an ECOG performance score of 0-1; and
3 There is documentation confirming that the disease does not express activating mutations of EGFR tyrosine kinases; and
4 Patient has documented disease progression following treatment with platinum based chemotherapy; and
5 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks.

Renewal application - only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1 No evidence of progressive disease according to RECIST criteria; and
2 The treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.
3 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks.

8.3 The Subcommittee **recommended** that nivolumab as monotherapy be funded with a medium/low priority for the treatment of patients with locally advanced or metastatic nonsquamous NSCLC that has progressed on or after prior platinum-based chemotherapy, subject to the following Special Authority criteria:

Nivolumab- PCT only - Specialist
Special Authority for Subsidy
Initial Application - only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1 Patient has locally advanced or metastatic nonsquamous non-small cell lung cancer; and
2 Patients has an ECOG performance score of 0-1; and
3 There is documentation confirming that the disease does not express activating mutations of EGFR tyrosine kinases; or
4 Patient has documented disease progression following treatment with platinum based chemotherapy; and
5 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks.

Renewal application - only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1 No evidence of progressive disease according to RECIST criteria; and
2 The treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.
3 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks.

8.4 The Subcommittee **recommended** that nivolumab as monotherapy be funded with a medium/low priority for the treatment of patients with EGFR mutation positive locally advanced or metastatic nonsquamous NSCLC that has progressed after both prior platinum-based chemotherapy and erlotinib or gefitinib, subject to the following Special Authority criteria:

> Nivolumab- PCT only - Specialist
> Special Authority for Subsidy
> Initial Application - only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1 Patient has locally advanced or metastatic nonsquamous non-small cell lung cancer; and
> 2 Patients has an ECOG performance score of 0-1; and
> 3 There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinases; and
> 4 Patient has documented disease progression following treatment with erlotinib or gefitinib; and
> 5 Patient has documented disease progression following treatment with platinum based chemotherapy; and
> 6 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks.
>
> Renewal application - only from a Medical Oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1 No evidence of progressive disease according to RECIST criteria; and
> 2 The treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.
> 3 Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 26 weeks.

8.5 Members noted that the priority of these recommendations was affected by the immaturity of evidence, low response rate and very high cost of treatment.

8.6 The Subcommittee has taken into account, where applicable, PHARMAC's relevant decision-making framework in relation to this recommendation.

Discussion

8.7 The Subcommittee noted that lung cancer was the leading cause of cancer death accounting for 19% of all cancer deaths and a third of all Māori cancer deaths in 2012. Members noted a correlation between lung cancer and social deprivation. The Subcommittee noted that NSCLC was the most common type of lung cancer and is subclassified as squamous and non-squamous which includes adenocarcinoma and large cell histologies. Members noted that NSCLC was a disease primarily occurring in the middle years and was more common in smokers.

8.8 The Subcommittee noted that in New Zealand the majority of patients, and higher proportions in Māori patients, presented with advanced stage IIIB or IV disease at diagnosis. Members noted that a large proportion of patients who are diagnosed with early stage disease eventually progress to advanced/metastatic disease.

8.9 The Subcommittee noted that for patients with advanced non-resectable nonsquamous NSCLC who have tested positive for epidermal growth factor

receptor (EGFR) tyrosine kinase activating mutations the current standard first-line treatment is with tyrosine kinase inhibitors erlotinib (Tarceva) or gefitinib (Iressa). The Subcommittee noted that, for patients with advanced non-resectable EGFR-negative NSCLC and squamous NSCLC, the current standard first-line treatment is with platinum-based chemotherapy.

8.10 The Subcommittee noted that for patients who progress on or after first-line treatment, platinum-based chemotherapy for EGFR positive patients or docetaxel for all other patients are the currently funded standard second-line treatment options.

8.11 The Subcommittee noted that survival rates for patients with advanced NSCLC were poor with currently funded treatments. Members considered that NSCLC was a uniformly fatal condition with few, if any, patients able to return to a normal life for any duration and because of this the prevalent patient population was relatively small. The Subcommittee considered patients with locally advanced or metastatic NSCLC had a high unmet health need.

8.12 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.

Squamous NSCLC

8.13 The Subcommittee noted that the key evidence for nivolumab for the treatment of squamous NSCLC comes from CHECKMATE-017 (CA209-017). This was a randomised, open-label, international phase III study of nivolumab compared with docetaxel in 272 patients with stage IIIb or IV squamous cell NSCLC who had disease recurrence after one prior platinum-containing regimen (Brahmer et al. N Eng J Med 2015;373:123-135).

8.14 The Subcommittee noted that patients were randomised to receive either nivolumab (3 mg/kg every 2 weeks, n=135) or docetaxel (75 mg/m2 every 3 weeks, n=137) until disease progression or discontinuation due to toxic effects or other reasons. Members noted that 90% of enrolled patients were current or former smokers.

8.15 The Subcommittee noted that at a minimum follow-up of 11 months, median overall survival (OS), the primary endpoint of the study, was 9.2 months (95% CI, 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel (HR for death 0.59; 95% CI 0.44 to 0.79; p<0.001) and the median progression-free survival (PFS) was 3.5 months (95% CI, 2.1 to 4.9) with nivolumab versus 2.8 months (95% CI, 2.1 to 3.5) with docetaxel (HR for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; p<0.001).

8.16 The Subcommittee noted the reported response rate was 20% (95% CI 14 to 28) with nivolumab versus 9% with docetaxel (95% CI 5 to 15; p=0.008). Members noted that the median duration of response was reported as 8.4 months with

docetaxel but not reached with nivolumab and considered this indicated early follow-up and immaturity of data.

8.17 The Subcommittee noted that PD-L1 protein expression was evaluated retrospectively in pretreatment but it was concluded by the authors that PDL1 expression was neither prognostic nor predictive of any of the efficacy endpoints. Members noted there appeared to be no biomarker for response in this population.

8.18 The Subcommittee noted that 7% of patients had grade 3 or 4 adverse events with nivolumab compared with 55% treated with docetaxel and the most frequent reported treatment-related grade 3 or 4 adverse events in the docetaxel group were neutropenia (30%), fatigue (8%) and febrile neutropenia (10%) and that no grade 4 adverse events were reported in the nivolumab group and three treatment related grade 3 adverse events were reported, one case each of tubulointerstitial nephritis, colitis and pneumonitis.

Nonsquamous NSCLC

8.19 The Subcommittee noted that the key evidence for nivolumab for the treatment of nonsquamous NSCLC comes from CHECKMATE-057 (CA209-057). This was a randomised, open-label, international phase III study of nivolumab in comparison with docetaxel in 582 patients with stage IIIb or IV or recurrent nonsquamous NSCLC after radiation therapy or surgical resection and disease progression during or after one prior platinum-based doublet chemotherapy regimen (Borghaei et al N Eng J Med 2015;373:1627-39).

8.20 The Subcommittee noted that patients were randomised to receive either nivolumab (3 mg/kg every 2 weeks, n=292) or docetaxel (75 mg/m2 every 3 weeks, n=290) until disease progression or discontinuation due to toxicity or other reasons.

8.21 The Subcommittee noted that enrolled patients with known EGFR mutation or anaplastic lymphoma kinase translocation were allowed to have received or be receiving an additional line of tyrosine kinase inhibitor therapy, and a continuation of or switch to maintenance therapy with pemetrexed, bevacizumab, or erlotinib was allowed in all patients. The Subcommittee noted that exclusion criteria included prior treatment with immune-stimulatory anti-tumour agents including checkpoint-targeted agents, or prior docetaxel therapy.

8.22 The Subcommittee noted that at a minimum follow up of 13.2 months, median OS, the primary end-point of the study, was reported to be 12.2 months (95% CI, 9.7 to 15.0) with nivolumab and 9.4 months (95% CI, 8.1 to 10.7) with docetaxel (HR for death, 0.73; 96% CI, 0.59 to 0.89; p=0.002). The Subcommittee noted that at one year the OS rate was 51% (95% CI, 45 to 56) with nivolumab and 39% (95% CI, 33 to 45) with docetaxel. The Subcommittee noted that the overall response rate (ORR) was 19% with nivolumab versus 12% with docetaxel (p=0.02).

8.23 The Subcommittee noted that grade 3 or 4 treatment-related adverse events were reported in 10% of patients in the nivolumab arm and 54% in the docetaxel

arm. The Subcommittee noted that the most frequently reported adverse events of any grade in the nivolumab arm were fatigue (16%), nausea (12%), decreased appetite (10%) and asthenia (10%) and in the docetaxel arm the most frequently reported adverse events of any grade were neutropenia (31%), fatigue (29%), nausea (26%) and alopecia (25%).

General comments

8.24 The Subcommittee noted that the evidence for the use of nivolumab in the treatment of locally advanced or metastatic NSCLC was from open-label studies, however, given the difficulties of conducting blinded studies in this population, considered the level of evidence to be of moderate to high strength and quality that was directly relevant to a New Zealand setting. However, members noted that the evidence was still developing and neither CHECKMATE-017 or CHECKMATE-057 were able to give statistical power to the calculations.

8.25 The Subcommittee considered that the current evidence indicated that for a small number of patients whose disease has progressed on or after platinum-based chemotherapy that treatment with nivolumab may provide a clinically meaningful response. The Subcommittee considered that the magnitude and duration of benefit from nivolumab over docetaxel was uncertain particularly due to the short length of follow-up in currently published literature.

8.26 Members considered that PDL1 expression may be an appropriate biomarker to target treatment to those nonsquamous NSCLC patients that would benefit most but noted that further data was needed regarding this.

8.27 The Subcommittee considered that the adverse event profile appeared quantifiable and managable but the management of patients receiving nivolumab treatment may require significant resources.

8.28 The Subcommittee considered that nivolumab as monotherapy should be funded for the treatment of locally advanced or metastatic squamous and nonsquamous NSCLC with a medium/low priority, taking into account the high health need of the patient population but noting the immaturity of the data, the limited and uncertain incremental benefit over current treatments, and the high price sought by the supplier.

9 Crisantaspase for acute lymphoblastic leukaemia

9.1 The Subcommittee considered a request from PHARMAC staff to provide feedback on the economic analysis of crisantapase (Erwinia L-asparaginase) for the treatment of patients with acute lymphoblastic leukaemia (ALL) who are allergic to asparaginase and/or pegaspargase, including clarification of the population likely to benefit from the treatment of crisantaspase. The Subcommittee was also invited to review its previous recommendations in relation to crisantaspase.

Recommendation

9.2 The Subcommittee **recommended** that crisantaspase be funded with a high priority for the treatment of patients with ALL or relapsed ALL who are allergic to asparaginase and/or pegaspargase, noting that ALL was a highly curable disease for which treatment was essential for survival but that crisantaspase was a very expensive treatment, subject to the following Special Authority criteria:

CRISANTASPASE
Initial Application - only from a Haematologist or Medical Oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Either
   1.1. Patient has acute lymphocytic leukaemia; or
   1.2. Patient has relapsed acute lymphocytic leukaemia as defined in a specified relapse protocol with curative intent; and
2. There is documentation that the patient is allergic to either L-asparaginase or pegaspargase; and
3. Treatment is to be given as part of a multi-agent protocol with curative intent.

Renewal Application - only from a Haematologist or Medical Oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Either
   1.1. Patient has acute lymphocytic leukaemia; or
   1.2. Patient has relapsed acute lymphocytic leukaemia as defined in a specified relapse protocol with curative intent; and
2. There is documentation that the patient is allergic to either L-asparaginase or pegaspargase; and
3. Treatment is to be given as part of a multi-agent protocol with curative intent; or

9.3 The Subcommittee **recommended** that crisantaspase be funded with a high priority for the second-line treatment of patients with lymphoblastic lymphoma and NK/T-cell lymphoma where treatment was part of a multi-agent protocol and given with curative intent and where patients are allergic to asparaginase and/or pegaspargase, subject to the following Special Authority criteria:

CRISANTASPASE
Initial Application - only from a Haematologist or Medical Oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following
1. Patient has lymphoblastic lymphoma or NK/T-cell lymphoma; and
2. There is documentation that the patient is allergic to either L-asparaginase or pegaspargase; and
3. Crisantaspase is to be used as second-line treatment as part of a multi-agent protocol with curative intent.

Renewal Application - only from a Haematologist or Medical Oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following
1. Patient has lymphoblastic lymphoma or NK/T-cell lymphoma; and
2. There is documentation that the patient is allergic to either L-asparaginase or pegaspargase; and
3. Crisantaspase is to be used as second-line treatment as part of a multi-agent protocol with curative intent.

9.4 The Subcommittee has taken into account, where applicable, PHARMAC's relevant decision-making framework in relation to this recommendation.

Discussion

9.5 The Subcommittee noted that crisantaspase is an asparaginase enzyme produced by the bacterium *Erwinia chrysanthemi* which is involved in the metabolism of the amino acid asparagine.

9.6 The Subcommittee noted that in March 2012 the Hospital Pharmaceuticals Subcommittee of PTAC had requested advice on the need for crisantaspase and pegasparaginase (a pegylated form of asparaginase) to be listed on the Hospital Medicines List.

9.7 The Subcommittee noted that L-asparaginase (Colaspase) produced from *E. coli* and pegaspargase are currently listed on the Hospital Medicines List.

9.8 The Subcommittee noted that it had previously considered the funding of crisantaspase in October 2012 and March 2013.

9.9 The Subcommittee noted the minute from its October 2012 meeting that crisantaspase was considered to be both more expensive and less efficacious than pegasparaginase; however that there was a small number of patients who demonstrate allergy or neutralising antibodies to L-asparginase (and would also be allergic to pegasparaginase) who would benefit from having crisantaspase available in the event of experiencing a 'significant allergic reaction' to either of these treatments.

9.10 The Subcommittee noted its previous recommendation from its March 2013 meeting that crisantaspase be included on the HML as there is good clinical evidence to support the use of crisantaspase in the second-line setting for patients who are allergic to L-asparaginase and pegaspargase restricted by the following criteria:

CRISANTASPASE
Initiation – haematologist and oncologist
Any of the following:
Either:
1. Patient has acute lymphocytic leukaemia and is allergic to either L-asparaginase or pegaspargase; or
2. Patient has relapsed acute lymphocytic leukaemia as defined in a specified relapse protocol with curative intent.

9.11 The Subcommittee noted that ALL is a haematologic malignancy that commonly presents in childhood and is subcategorised based to lineage of cells as either B cell or T cell. The Subcommittee noted that patients with ALL lack an enzyme which synthesises the amino acid asparagine and rely on external sources of asparagine for cell growth and survival.

9.12 The Subcommittee noted that treatment for most patients with ALL is given with curative intent and that approximately 60% of ALL patients were young and required extended periods of treatment. Members considered that ALL was a highly curable form of cancer which made effective treatment options essential.

9.13 The Subcommittee noted that currently funded treatments for ALL are L-asparginase and pegasparagase, although the majority of patients receive pegasparagase due to its higher efficacy and more durable treatment effect. The Subcommittee noted that the survival rate with these agents is more than 90%;

however, a minority of patients, around 3%, develop antibodies and have allergic reactions to these treatments. Members noted that patients typically do not have allergic reactions to their first dose and that allergy can develop on any subsequent dose.

9.14 The Subcommittee considered that it was not possible to reliably measure asparagine levels as it degrades very quickly in the blood stream, nor was the measurement of asparagine antibodies a good indicator of asparagine levels due to its lack of specificity. Members considered that the only way to identify those patients who were allergic to L-asparaginase was when a patient had an allergic reaction to the agent.

9.15 The Subcommittee noted that approximately 10%-20% of patients with ALL relapse; however, very few of them receive further treatment with curative intent.

9.16 The Subcommittee noted that crisantaspase is used in ALL relapse protocols for both adult and paediatric patients where treatment is with curative intent and patients have allergic reactions to L-asparginase or pegasparagase at any stage of treatment. Members noted that allergic reaction to crisantaspase is lower than with the currently funded treatments.

9.17 The Subcommittee noted that the dose in standard protocols for ALL treatment varies widely. Members considered that dose equivalence for crisantaspase was generally six-times the pegaspargase dose and that doses of up to 20-25,000 iu were appropriate for some protocols.

9.18 The Subcommittee considered that the use of crisantaspase could reduce the number of bone marrow or stem cell transplants for patients with ALL.

9.19 The Subcommittee considered that the evidence for the use of crisantaspase in the treatment of ALL was of moderate strength and quality.

9.20 The Subcommittee noted that crisantaspase would likely provide similar rates of cure and 5 year survival as L-asparginase or pegaspargase protocols.

9.21 The Subcommittee noted that NPPA applications had been received for crisantaspase or pegaspargase for patients with other types of lymphoma, including NK/T cell lymphoma and peripheral T cell lymphoma.

9.22 The Subcommittee noted that all patients with allergic reactions to asparaginase, not just patients with ALL, would likely benefit from treatment with crisantaspase but this agent should only be used with curative intent. The Subcommittee noted that, in addition to ALL, crisantaspase would provide benefit for patients with lymphoblastic leukaemia, NK/T cell leukaemia and a small number of relapsed ALL patients where treatment was part of a multi-agent protocol and given with curative intent.

9.23 The Subcommittee considered that approximately 6-10 patients per year would potentially seek treatment with crisantaspase; however, the majority of these patients would be paediatric and could receive treatment under the paediatric PCT pathway.