Subsidised access to new melanoma drugs: in need of further innovation?

Michael Wonder, Rosalie Fisher

ABSTRACT

AIMS: Melanoma is the most serious of the three common forms of skin cancer. New Zealand and Australia have the highest melanoma incidence rate in the world. A number of new treatments for melanoma with different modes of action have recently become available. Our aim was to examine their availability and subsidized access in New Zealand and to compare their availability and access in Australia and England.

METHODS: We examined the clinical evidence base of the new treatments, their place in treatment guidelines and their consideration for reimbursement by PHARMAC in New Zealand, the PBAC in Australia and NICE in England.

RESULTS: The PBAC and NICE have recommended most treatments and their recommendations have been implemented promptly, using innovative access and pricing models. PHARMAC has rejected most of the new treatments and none has been funded. Pembrolizumab has been recommended with a low priority.

CONCLUSIONS: New Zealand should not be in the unenviable position whereby it has the highest incidence of a fatal disease yet is the last country in the Western world to fund effective treatments for it. We offer recommendations to all stakeholders to break the current access impasse.

Malignant melanoma is a cancer of the skin and is the most serious of the three common forms of skin cancer. Although melanoma is more often diagnosed in older people, it is increasingly affecting younger people.1

Metastatic melanoma is life-threatening and is associated with low survival rates;2 approximately one out of every five people will survive for five years following a diagnosis with late-stage disease.3 There are about 200,000 new cases of melanoma diagnosed worldwide each year.4

New Zealand and Australia have the highest melanoma incidence rate in the world; respectively, more than 4,000 and 11,000 new cases of melanoma are registered annually. Metastatic melanoma results in significant loss of life in both countries: more than 300 New Zealanders die of melanoma each year,5 and in Australia in 2012 there were more than 1,500 deaths from melanoma.6 Key strategies to prevent melanoma deaths are prevention, early detection and effective therapies for advanced disease.

For decades, the treatment options for patients with metastatic melanoma were few and of limited efficacy. The median overall survival of nine months had not changed in 30 years. A number of new treatments for patients with metastatic melanoma have become available in the past four years. They are all targeted treatments with new modes of action; they are more effective but also more costly, and are set to revolutionise the treatment of patients with metastatic melanoma.

Our objective was to examine the availability and subsidised access of these new medicines by melanoma patients in New Zealand and to compare their availability and access in Australia and England.

Epidemiology

Cutaneous malignant melanoma is a tumour of melanocytes in the basal layer of the epidermis. Risk factors for the development of melanoma include skin phototype, UV exposure, and genetic predisposition and thus it most common in Caucasian populations, such as those of
Australasia, North America, and Northern Europe.\(^7\)

Melanoma is a particular health concern in Australia and New Zealand—countries with the highest global incidence of melanoma—and in the United Kingdom, where the incidence of melanoma has risen more rapidly over the last 30 years than those of the 10 most common cancers.\(^8\)

In 2011, the age-standardised incidence rate (ASR) of cutaneous melanoma in Australia was 48 cases per 100,000 persons and from 2011 to 2013, the ASR was 37 per 100,000 in New Zealand.\(^6,9\) In Australasia, melanoma is the fourth most common cancer (defined by the total number of cases), and in the UK, the fifth.

Importantly, in all three countries, melanoma disproportionately affects a younger group of patients; for example, it is the most common cancer to affect the 15–24 age group in Australia.\(^6\) Consequently, mortality from melanoma results in greater loss of potential years than from other cancers in the US, an average of 20.4 years compared to 16.6 years per individual.\(^10\)

### Biology

Melanoma is staged according to the TNM classification, with stage groupings determined by thickness, ulceration and mitotic count and the presence of regional nodal metastases and metastatic disease.\(^11\) Currently, the use of systemic treatments in melanoma is confined to patients with inoperable stage 3, or stage 4, melanoma.

Distinct sub-types of melanoma are now recognised, which differ by aetiology, clinicopathological features and driver gene mutations. The observation that up to 50% of melanomas harbour a somatic mutation in the \(BRAF\) (v-raf murine sarcoma viral oncogene homolog B1) gene was the foundation upon which a new drug class has been developed;\(^12\) subsequently, a number of genotypes, correlating with site of melanoma origin and/or degree of UV exposure, were described among primary melanomas.\(^13,14\)

In cutaneous melanomas, mutations resulting in aberrant signaling of the mitogen-activated protein kinase (MAPK) pathway such as \(BRAF\) and \(NRAS\) (neuroblastoma RAS viral (v-ras) oncogene homolog) mutations, are frequent. Mutations of codon 600 in the kinase domain of the \(BRAF\) gene account for 80% of mutations (most commonly V600E and V600K mutations) and all activate this important growth pathway. Currently, the tumoural \(BRAF\) status (mutant versus wild-type) is the only factor that influences systemic treatment type in advanced melanoma.

Another important biological feature of melanoma is that it is the most highly mutated of the haematological and solid organ malignancies.\(^15\) It is postulated that the somatic mutation burden of melanoma results in a large number of antigens presented to the immune system and might account for the greater success of immunotherapies in this disease compared to other cancers.

The clinical course of metastatic melanoma is varied—the degree of immune control is widely speculated to account for the differences observed between patients—but it is inevitably fatal and, for many patients, leads to rapid deterioration and death.

Common sites of metastases are the skin, lymph nodes, lung, liver and brain and an individual’s last months are typically highly morbid. The treatment intent remains one of palliation.

### Current treatments

Up until 2011, the treatment options for patients with malignant melanoma were the alkylating agents dacarbazine (DTIC) and fotemustine and the antimicrotubule agent paclitaxel. Dacarbazine is indicated for the treatment of metastatic melanoma, whereas fotemustine is indicated for disseminated melanoma including cerebral metastases.

Dacarbazine and fotemustine have been trialled extensively and have complete and partial response rates of around 10%. They do not prolong survival.\(^16,17\)

Major improvements in the understanding of the biology of melanocytes and the drivers of their growth have led to the development of new agents with novel modes of action (Tables 1 and 2).
MAPK pathway inhibitors: BRAF and MEK inhibitors

The BRAF inhibitors vemurafenib and dabrafenib mesylate are selective inhibitors of mutant BRAF. In their phase III registration trials, both agents were compared to dacarbazine in previously untreated patients with advanced V600E mutated melanoma and both demonstrated marked superiority.18,19 Vemurafenib and dabrafenib mesylate appear to have similar efficacy in these trials although they have not been compared directly (Table 2). Both treatments are oral and have acceptable toxicity profiles, although these differ somewhat. Owing to their high response rates, rapid onset of action and activity in the central nervous system,20 the BRAF inhibitors are viewed as highly effective palliative treatments in the treatment of patients with advanced melanoma, including those with poor performance status. However, multiple mechanisms of resistance to these drugs are now described,21 and long-term survivors treated with these drugs alone are in the minority.

Trametinib dimethyl sulphoxide is an oral, selective inhibitor of MEK1 and MEK2 (MAPK/ERK kinase 1 and 2). In a randomised phase III trial, trametinib dimethyl sulphoxide monotherapy was superior to dacarbazine or paclitaxel in untreated patients with BRAF V600E or V600K mutant melanoma but the treatment benefit in this population is modest compared to the BRAF inhibitors.21

There are now substantial data indicating that the MAPK pathway remains activated in patients with clinical resistance to the BRAF inhibitors.22 Thus, combination BRAF and MEK inhibitor treatment was trialed in an attempt to lengthen the duration of control provided by BRAF inhibitors alone. Three phase III trials have established superiority of combination treatment over BRAF inhibitor monotherapy.23,24,25 All trials were undertaken in the first-line setting; the first two studied the combination of dabrafenib mesylate and trametinib dimethyl sulphoxide, compared to dabrafenib mesylate or vemurafenib monotherapy;23,24 and the third, combination vemurafenib with the MEK inhibitor cobimetinib against vemurafenib alone.25 Each trial found a consistent and significant benefit in response rates and progression-free survival in favour of combination treatment. Overall survival data are not mature in the vemurafenib and cobimetinib trial but the others demonstrated a clear reduction in the risk of death with combination treatment. These findings, along with the observation that combination BRAF and MEK inhibition may be less toxic than BRAF inhibitor monotherapy,23 have established combination treatment for BRAF mutant melanoma as the new standard of care.

Immune checkpoint inhibitors

Ipilimumab is a humanized monoclonal antibody targeting the cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor, a negative co-stimulatory molecule expressed on effector and regulatory T cells.26

In two phase III trials evaluating pre-treated and treatment-naïve patients,26,27 ipilimumab resulted in prolongation of overall survival compared to the gp100 vaccine or chemotherapy treatment, although response rates to this agent are low. Recently, data from the phase III trials have been analysed along with phase II data, finding a median overall survival of 11.5 months for patients with advanced melanoma treated with ipilimumab, but, more importantly, that the survival curves for these patients starts to plateau at three years, confirming that longer-term survival after this treatment is possible in responders.28 Ipilimumab can cause serious immune-related side effects affecting the skin, gastro-intestinal tract, liver and endocrine glands.

Pembrolizumab and nivolumab inhibit a different immune checkpoint receptor, Programmed Death-1 (PD-1), whose interaction with ligands PD-L1 and PD-L2 found on tumour and antigen-presenting cells down-regulates T-cell activation. Nivolumab has been compared to chemotherapy as first-line treatment in patients with BRAF wild-type metastatic melanoma, offering significantly higher response and one-year survival rates.29 Both nivolumab and pembrolizumab are superior to chemotherapy after failure of anti-CTLA-4 therapy.30,31,32 Pembrolizumab and ipilimumab were directly compared as first-line treatments of advanced melanoma (KN-006 trial) and pembrolizumab was unequivocally more efficacious than ipilimumab,
as well as having an improved toxicity profile.\textsuperscript{24} This important study has strongly influenced treatment guidelines and was highly relevant to the regulatory and reimbursement process for pembrolizumab in some countries.

The most impressive activity of immune checkpoint inhibitors in metastatic melanoma patients was observed in the phase III trial of combination nivolumab and ipilimumab, versus nivolumab or ipilimumab monotherapy.\textsuperscript{29} The median progression-free survival in the combination arm was 11.5 months, compared to 6.9 months and 2.9 months in the nivolumab and ipilimumab arms respectively. This trial did not address the issue of combination versus sequential immunotherapy.

In summary, there are now more than 10 phase III randomised, controlled trials supporting the use of BRAF, MEK and immune checkpoint inhibitors to prolong life in patients with metastatic melanoma. These trials predominantly treat regimens with the same mode of action, and the focus of much research and debate currently is the optimal sequencing of MAPK inhibitors and immunotherapies. Although randomised trial evidence comparing different sequences is not available, clinical practice is informed by data indicating that immune checkpoint inhibitors appear to be effective following kinase inhibitor therapy, and vice versa.\textsuperscript{34,35} Additionally, the melanoma genotype, the clinical status of the patient and the registered indication for each agent are all factors in determining the order of systemic treatment. While combinations within the classes of kinase inhibitors and immune checkpoint inhibitors are effective and safe, use of BRAF and/or MEK inhibitors with immunotherapy remains experimental.

Further information on these new treatment options are provided in Table 1.

### Treatment guidelines

Treatment guidelines from the US and Europe are the most relevant, as these incorporate the major drug developments in metastatic melanoma that have occurred since 2010. Australasian and British

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**Table 1: New treatments for patients with metastatic melanoma.**

<table>
<thead>
<tr>
<th>Medicine (generic name)</th>
<th>Ipilimumab</th>
<th>Vemurafenib</th>
<th>Dabrafenib mesylate</th>
<th>Trametinib dimethyl sulfoxide</th>
<th>Cobimetinib</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine (brand name)</td>
<td>Yervoy</td>
<td>Zelboraf</td>
<td>Tafinlar</td>
<td>Mekinist</td>
<td>Cotelix</td>
<td>Keytruda</td>
<td>Opdivo</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Bristol-Myers Squibb (BMS)</td>
<td>Roche</td>
<td>GlaxoSmithKline (GSK)*</td>
<td>GlaxoSmithKline (GSK)*</td>
<td>Roche</td>
<td>Merck, Sharp &amp; Dohme (MSD)</td>
<td>Bristol-Myers Squibb (BMS)</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Checkpoint inhibitor</td>
<td>BRAF inhibitor</td>
<td>BRAF inhibitor</td>
<td>MEK inhibitor</td>
<td>MEK inhibitor</td>
<td>Programmed death 1 inhibitor</td>
<td>Programmed death 1 inhibitor</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Parenteral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Date of approval (EU)</td>
<td>13/07/2011</td>
<td>17/02/2012</td>
<td>26/08/2013</td>
<td>30/06/2014</td>
<td>20/11/2015</td>
<td>17/07/2015</td>
<td>19/06/2015</td>
</tr>
<tr>
<td>Date of approval (Australia) (ARTG Start Date)</td>
<td>4/07/2011</td>
<td>10/05/2012</td>
<td>27/08/2013</td>
<td>14/02/2014</td>
<td>Not registered</td>
<td>16/04/2015</td>
<td>11/01/2016</td>
</tr>
<tr>
<td>Date of approval (New Zealand)</td>
<td>22/03/2012</td>
<td>16/02/2012</td>
<td>19/06/2014</td>
<td>26/03/2015</td>
<td>Not registered</td>
<td>3/09/2015</td>
<td>28/04/2016</td>
</tr>
</tbody>
</table>

Registered patient populations (New Zealand):

- Advanced (unresectable or metastatic) melanoma, first-line
- Advanced (unresectable or metastatic) melanoma, BRAF V600 mutation positive
- Advanced (unresectable or metastatic) melanoma, BRAF V600 mutation positive, monotherapy AND Advanced (unresectable or metastatic) melanoma, BRAF V600 mutation positive, combination (dabrafenib mesylate)
- Not registered
- Advanced (unresectable or metastatic) melanoma, monotherapy
- Advanced (unresectable or metastatic) melanoma, monotherapy AND advanced (metastatic) melanoma, combination (ipilimumab)

* Current sponsor is Novartis
Table 2: Selected clinical trial data for newly approved treatments for metastatic melanoma.

<table>
<thead>
<tr>
<th>Medicine (generic name)</th>
<th>Ipilimumab</th>
<th>Vemurafenib</th>
<th>Dabrafenib mesylate</th>
<th>Trametinib dimethyl sulphoxide</th>
<th>Cobimetinib</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial design</td>
<td>Phase III; randomised</td>
<td>Phase III; randomised</td>
<td>Phase III; randomised</td>
<td>Phase III; randomised (in combination with vemurafenib)</td>
<td>Phase III; randomised; first-line</td>
<td>Phase III; randomised; first-line</td>
<td></td>
</tr>
<tr>
<td>Patient population</td>
<td>1. Previously treated unresectable stage IIIC or stage IV melanoma 2. First-line treatment unresectable stage IIIC and stage IV melanoma</td>
<td>First-line treatment unresectable stage IIIC and stage IV BRAF mutant melanoma</td>
<td>First-line treatment unresectable stage IIIC and stage IV BRAF mutant melanoma*</td>
<td>First-line monotherapy unresectable stage IIIC and stage IV BRAF mutant melanoma</td>
<td>First-line treatment unresectable stage IIIC and stage IV melanoma</td>
<td>First-line treatment BRAF-wild type melanoma</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>1. gp100 peptide vaccine 2. Chemotherapy</td>
<td>Dacarbazine</td>
<td>Dacarbazine</td>
<td>Chemotherapy</td>
<td>Vemurafenib</td>
<td>Ipilimumab</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>1. 10.9 vs 1.5 2. 15.2 vs 10.3</td>
<td>48 vs 5</td>
<td>50 vs 7</td>
<td>22 vs 8</td>
<td>68 vs 45</td>
<td>33.7 vs 11.9</td>
<td>40 vs 13.9</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>1. 2.86 vs 2.76 2. Not available</td>
<td>5.3 vs 1.6</td>
<td>5.1 vs 2.7</td>
<td>4.8 vs 1.5</td>
<td>9.9 vs 6.2</td>
<td>5.5 vs 2.8</td>
<td>5.1 vs 2.2</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>1. 10 vs 6.4 2. 11.2 vs 9.1</td>
<td>13.6 vs 9.7</td>
<td>Not available</td>
<td>Not available</td>
<td>22.3 vs 17.4</td>
<td>Not reached</td>
<td>Not reached vs 10.8</td>
</tr>
<tr>
<td>Toxicities</td>
<td>Immune-related skin, gastrointestinal, hepatic</td>
<td>Cutaneous including photosensitivity, fatigue, arthralgia</td>
<td>Cutaneous, pyrexia, fatigue, arthralgia</td>
<td>Cutaneous, diarrhea, fatigue, oedema</td>
<td>Fatigue, cutaneous, pyrexia, arthralgia, gastrointestinal</td>
<td>Fatigue, pruritus, rash, immune-related</td>
<td>Fatigue, pruritus, nausea, immune-related</td>
</tr>
</tbody>
</table>

*Also studied in combination with dabrafenib mesylate in two randomised phase III trials

PFS = progression-free survival, OS = overall survival.

clinical practice guidelines advise the use of chemotherapy, palliative care or clinical trial participation for metastatic melanoma patients.36,37 However, national standards for the treatment of patients with melanoma in New Zealand recommend the availability of BRAF and immune checkpoint inhibitor therapy for these patients.38

More specifically, the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines discuss the preferred sequence of drug therapy.39,40 For patients who are rapidly deteriorating, both guidelines advocate pembrolizumab, nivolumab or BRAF and MEK inhibitors (the latter in those with BRAF mutant melanoma), owing to the higher response rates of these agents. Ipilimumab is reserved for those who are clinically stable or following kinase inhibitor treatment, where the treatment intent is long-term survival. For BRAF wild-type patients, pembrolizumab, nivolumab and ipilimumab are all accepted as first-line treatments but the ESMO Guidelines go further in stating that pembrolizumab is preferred due to its superior efficacy against ipilimumab and improved tolerability. It is worth noting that both guidelines support the use of kinase and immune checkpoint inhibitors in patients with brain metastases.

**Prices**

The prices of the current treatments in the US, England and Australia are provided in Table 3. They should be considered as indicative insofar as they are not expressed in the same currency and price level (eg, ex-manufacturer price). In many instances, the net reimbursed price is lower. Insofar as these medicines are expensive and beyond the purchasing capacity of most people with melanoma, reimbursement is essential to ensure patient access.

**Reimbursement status (New Zealand)**

The medicine reimbursement program in New Zealand, including the role of PHARMAC, is summarised in Table 4. Dacarbazine has been listed in Section B of the New Zealand Pharmaceutical Schedule since 2005.44
Vemurafenib

Roche lodged a submission with PHARMAC on 22 November 2011 for vemurafenib, seeking its listing in the New Zealand Pharmaceutical Schedule for patients with unresectable stage IIIC or stage IV melanoma positive for a BRAF V600 mutation.

The submission was considered by the PTAC in February 2012. “The Committee considered that overall vemurafenib was a very high cost treatment that provided only a small, short term, benefit.”

The submission was referred to the Cancer Treatments Subcommittee (CaTSoP) who considered it the following month. “The Subcommittee recommended that vemurafenib should be funded for patients with unresectable stage IIIC or stage IV melanoma positive for BRAF V600 mutation. Because of the high cost of vemurafenib and the short-term evidence, members gave this recommendation a low priority. Members noted that if the price of vemurafenib were to significantly decrease, its priority rating may improve.”

In the light of CaTSoP’s recommendation, the submission was considered by the PTAC again in May 2012. “The Committee considered that there were few funded alternatives available and that vemurafenib improved the treatment of melanoma in this setting. Overall, the Committee considered that it would maintain its previous recommendation, that this application for vemurafenib should be declined because it only provided only a small benefit for a very high cost.”

Roche is yet to lodge a resubmission.44

Ipilimumab

Bristol-Myers Squibb lodged a submission for ipilimumab on 21 May 2012 seeking a listing in the Schedule for patients with previously treated unresectable stage IIIC or IV melanoma.

The submission was considered by the PTAC in August that year. “The Committee noted that ipilimumab was a very expensive treatment, and considered that the non-specific immune activation related toxicity of ipilimumab was too hazardous to justify the uncertain incremental benefits at the price offered. The Committee recommended that the application be declined. The Committee further recommended that the application be considered by the Cancer Treatments Subcommittee.”

The submission was considered by the CaTSoP in October 2012. “The Subcommittee considered that overall the evidence was relatively strong for ipilimumab providing a small increase in median overall survival. However, the evidence was very weak for any long-term benefit. Members considered that the evidence at this time indicated that the autoimmune effects of ipilimumab were too hazardous to justify the small, and uncertain, benefit at the price being offered. Therefore, the subcommittee recommended that the application be declined.”

Table 3: Prices of the new treatments for melanoma.41,42,43

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Ipilimumab</th>
<th>Vemurafenib</th>
<th>Dabrafenib mesylate</th>
<th>Trametinib dimethyl sulphoxide</th>
<th>Cobimetinib</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>US*</td>
<td>$7,200 (50 mg vial) (AWP)</td>
<td>$47 (240 mg tablet) (AWP)</td>
<td>$9,120 (120 capsules) (AWP)</td>
<td>$348 (2 mg tablet) (AWP)</td>
<td>~$6,000 (cycle) (WAC)</td>
<td>$2,158 (50 mg vial) (AWP)</td>
<td>$12,500/mo (AWP)</td>
</tr>
<tr>
<td>England**</td>
<td>£3,750 (50 mg vial)</td>
<td>£1,750 (56 x 240 mg tablets)</td>
<td>£933.33 (28 x 50 mg capsules)</td>
<td>Not available</td>
<td>£4275.67 (63 x 20 mg tablets)</td>
<td>£1,315 (50 mg vial)</td>
<td>£349 (40 mg vial), £1097 (100 mg vial)</td>
</tr>
<tr>
<td>Australia***</td>
<td>$48,159.70 (360 mg)</td>
<td>Not available</td>
<td>$5,888.32 (120 x 50 mg capsules)</td>
<td>$8,759.04 (30 x 2 mg tablets)</td>
<td>Not available</td>
<td>$11,426.36 (240 mg)</td>
<td>$7559.52 (360 mg)</td>
</tr>
</tbody>
</table>

* Price at launch; ** Price as stated in the British National Formulary; ***PBS list prices. AWP = average wholesale price, WAC = wholesale acquisition cost.

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Bristol-Myers Squibb lodged a resubmission that was considered by the PTAC in February 2014. “The Committee recommended that the application be declined.

“The Committee further recommended that the application be referred to the Cancer Treatments Subcommittee for review once longer-term data from the randomised study had been provided.

“The Committee considered it likely that ipilimumab was associated with some long term survival advantage over best supportive care but remained uncertain of the magnitude of benefit.”

Bristol-Myers Squibb is yet to provide the longer-term data to PHARMAC. These data are now in the public domain.

Dabrafenib mesylate
GlaxoSmithKline has lodged a submission for dabrafenib mesylate seeking its listing in the Schedule for patients with BRAF V600 mutation-positive stage III or stage IV malignant melanoma.

“The Committee recommended that the application for dabrafenib for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma be declined.”

“The Committee considered given the high unmet need for effective treatments for metastatic melanoma it would be appropriate for one of vemurafenib, ipilimumab or dabrafenib to be funded. Members noted that all three treatments had been recommended for decline primarily due to their very poor cost effectiveness at the proposed prices. The Committee considered that all three offered some clinical benefit and recommended that PHARMAC run a competitive process to enable one of these treatments to be funded if reasonably cost effective.”

The sponsorship of dabrafenib mesylate was transferred to Novartis on 9 September 2015.

Pembrolizumab
On 18 September 2015, the CaTSoP considered an application from MSD for the funding of pembrolizumab for the treatment of patients with metastatic or unresectable stage III or IV melanoma. The Subcommittee recommended that pembrolizumab should be funded for the treatment of metastatic or unresectable melanoma stage III or IV with low priority. The Subcommittee noted that the low

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Table 4: Reimbursement/health technology assessment (HTA) agencies in New Zealand, Australia and England.42,43,44

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>New Zealand</th>
<th>Australia</th>
<th>England</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment agency</td>
<td>Pharmaceutical Management Agency (PHARMAC)</td>
<td>Pharmaceutical Benefits Advisory Committee (PBAC)</td>
<td>National Institute for Health and Care Excellence (NICE)</td>
</tr>
<tr>
<td>Technologies assessed</td>
<td>Medicines, vaccine, blood products, devices</td>
<td>Medicines, vaccines</td>
<td>Medicines, devices, procedures</td>
</tr>
<tr>
<td>Commencement of subsidised access</td>
<td>When listed in the New Zealand Pharmaceutical Schedule</td>
<td>When listed in the Schedule of Pharmaceutical Benefits</td>
<td>Within 90 days of the publication of a positive Final Appraisal Determination (FAD)</td>
</tr>
<tr>
<td>Submissions considered before local registration</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Subsidised access possible before local registration</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Early access scheme for emerging new medicines</td>
<td>No</td>
<td>Managed entry scheme</td>
<td>Patient access scheme</td>
</tr>
</tbody>
</table>
priority rating was influenced by the early evidence base, and the consequent uncertainty about its longer term benefits and potential risks, as well as its very high cost.

The PTAC considered the submission at its November 2015 meeting. The Committee recommended that pembrolizumab be funded for the treatment of metastatic or unresectable stage III or IV melanoma with a low priority.

At the November meeting, the Committee also noted that it may reconsider the funding of ipilimumab, including a review of the recently published long term follow-up data.44

Trametinib dimethyl sulphoxide, nivolumab

PHARMAC is yet to announce that it has received a funding application for these medicines (see footnote).44

**Reimbursement status (Australia)**

The Australian medicine reimbursement program, the Pharmaceutical Benefits Scheme, is summarised in Table 4.

The PBAC has established a process with the Medical Services Advisory Committee (MSAC) to enable the rapid assessment of co-dependent technologies.46

Dacarbazine is not listed on the PBS. Fotemustine was listed on the PBS on 1 April 2005 for patients with metastatic disease.43

**Ipilimumab**

The PBAC has considered multiple submissions to list ipilimumab on the PBS for the treatment of patients with stage III or stage IV malignant melanoma. The first two submissions (July 2011 & March 2012) were rejected due to concerns about the clinical place of ipilimumab in therapy and other reasons.

A third submission was considered in November 2012. The PBAC noted that the sponsor’s expert advisory panel considered a requirement to use dacarbazine or fotemustine to be contrary to clinical judgment and would therefore be unlikely to be observed in practice.

The PBAC concluded that a requirement for patients to first try then fail ineffective and toxic first-line chemotherapy would not be clinically appropriate and requested that the PBS restriction be developed so as to permit the first-line use of ipilimumab.

The PBAC noted the high unmet clinical need for treatments for metastatic melanoma with proven survival advantage.

The PBAC noted that the cost effectiveness of ipilimumab is highly dependent on the duration of survival. Although concerned about the cost-effectiveness of ipilimumab if the claimed survival gain were not observed in practice, the Committee recommended the listing of ipilimumab for metastatic melanoma, subject to risk-share arrangements involving appropriate use, maintaining cost-effectiveness and managing financial risk.

Ipilimumab was listed in the Schedule of Pharmaceutical Benefits for patients with stage III or stage IV melanoma on 1 August 2013.43

**Vemurafenib**

The PBAC has considered two submissions to list vemurafenib on the PBS for use by patients with stage IIIIC or stage IV melanoma positive for a BRAF V600 mutation. The first submission was deferred by the PBAC in July 2012 in order to obtain further information from the applicant and the MSAC on the following:

- Unacceptable cost effectiveness
- Negotiation of a risk-share agreement
- Further specification of the target patient population and the associated PBS restrictions
- Further revisions to the modeled economic evaluation and their effect on the ICER (applicant)
- Advice on the disease stage at which subsidised testing should occur, the total number of tests, the number of tests per patient reflecting the frequency of repeat testing, the costs of testing per patient treated with vemurafenib, and the cost of testing for resistance

The PBAC considered a resubmission for vemurafenib at its meeting in March 2013.

The PBAC deferred the resubmission in order for the Department of Health to consider an appropriate arrangement for data collection and to enable the Department to negotiate an appropriate price.
The PBAC made reference to the recent recommendation for ipilimumab and the submission for dabrafenib mesylate that was also considered for PBS listing at the March 2013 meeting. The PBAC intended to conclude that, on balance, vemurafenib and dabrafenib mesylate are clinically non-inferior to each other, and so should be cost-minimised against each other.

Roche is yet to lodge another submission so vemurafenib is not listed on the PBS.43

The interplay between the PBAC and the MSAC in relation to access to BRAF mutation testing is outlined in Figure 1.

Dabrafenib mesylate

The PBAC considered a submission to list dabrafenib on the PBS for the treatment of patients with BRAF V600 mutation positive stage IIIC or stage IV melanoma in March 2013. The submission was considered under the TGA/PBAC parallel process; under the TGA-PBAC parallel processes, a submission to the PBAC may be lodged at any time from the date of lodgement of a TGA registration dossier.

The PBAC deferred the submission in order to be informed of the TGA delegate’s proposed registration and rationale, to enable the Department of Health to consider an appropriate arrangement for data collection and to negotiate an appropriate price.

A re-submission, that included a revised pricing proposal, was considered by the PBAC in July 2015. The PBAC recommended the PBS listing of dabrafenib mesylate that become effective on 1 December 2013 with a special pricing arrangement.43

Trametinib dimethyl sulphoxide

In March 2014, the PBAC considered a submission to listing trametinib dimethyl sulphoxide on the PBS for use in combination with dabrafenib mesylate by patients with BRAF V600 mutation positive stage III or stage IV melanoma.

The PBAC rejected the submission on the basis that the superior comparative effectiveness of trametinib dimethyl sulphoxide with dabrafenib mesylate over dabrafenib mesylate monotherapy had not been established.43

Figure 1: Access to BRAF testing.47

MSAC consideration of BRAF testing for vemurafenib and dabrafenib mesylate

2 August 2012

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of BRAF testing to help determine eligibility for proposed PBS-subsidised vemurafenib in unresectable stage IIIC or stage IV metastatic cutaneous melanoma, MSAC deferred the application until its responses to PBAC’s requests for advice and further information from the applicant are considered by PBAC. If PBAC refers more matters to MSAC for advice, MSAC will reconsider these referrals.

If PBAC subsequently decides to recommend to the Minister that vemurafenib be listed on the PBS, MSAC will support an expedited process for its reconsideration to align its support for public funding of BRAF testing according to the circumstances recommended by PBAC.

5 April 2013

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of BRAF V600 mutation testing to help determine eligibility for proposed PBS-subsidised vemurafenib in unresectable stage III or stage 4 metastatic cutaneous melanoma, MSAC deferred the application until PBAC reconsideres the PBS listing of vemurafenib. MSAC noted that this might be associated with a PBAC reconsideration of dabrafenib, an alternative BRAF inhibitor.

1 August 2013

“After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of BRAF mutation testing to help determine eligibility for proposed PBS-subsidised dabrafenib in unresectable Stage III or Stage IV metastatic cutaneous melanoma, MSAC supports its public funding via a new MBS item, with an MBS fee of $230.95 and an item descriptor of:

A test of tumour tissue from a patient with unresectable stage III or stage IV metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to BRAF V600 mutation status for access to dabrafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC also reaffirmed its April 2013 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected prospectively to be reviewed two years after listing.”
The PBAC noted that, following lodgement of the submission on 5 November 2014, an extraordinary amount of important additional information was provided throughout the process of evaluation, including:

- 24 November 2014: trial data from KN-002 provided by the sponsor (20 slides)
- 28 January 2015: revised model and revised managed entry scheme (MES) proposal with the PSCR (16 pages)
- 13 February 2015 (after the ESC meeting): early results of KN-006 provided by the sponsor (38 pages) (KN-006 = randomised trial data directly comparing pembrolizumab with ipilimumab in ipilimumab naïve patients)
- 17 February 2015: TGA delegate’s overview provided by the sponsor (96 pages)
- 25 February 2015: Attachment and PES Addendum to the ESC Advice to comment on the additional post-submission information (20 pages)
- 4 March 2015: further sensitivity analyses for the revised model and suggestions for the MES proposal with the pre-PBAC response (24 pages)
- 6 March 2015: additional information provided by the sponsor on proposed subsidised access to pembrolizumab for ipilimumab refractory patients via a funding arrangement from the sponsor (2 pages)

Thiswas in addition to five meetings with the Department before the submission was lodged (3 December 2013, 13 May 2014, 27 August 2014, 28 August 2014, and 5 September 2014) and two post-submission meetings (10 December 2014 and 2 March 2015) between the sponsor and the Department.

The provision of extraordinarily large post-submission documents had placed an unreasonable pressure on the PBAC’s supporting processes, and evaluation capacity, particularly just prior to the PBAC meeting. As a consequence, there was insufficient time to comprehensively evaluate all the material provided, and address relevant matters such as the open-label design, the potential for differences in drop-out rates between the trial arms, and the difference between the pembrolizumab dosage regimens in KN-006 and the dosage regimen requested for TGA approval and PBS subsidy. Also, since much of the material relating to KN-006 was accepted as being provided on a confidential basis, it would be redacted from the published version of the PBAC Outcomes document and of the Public Summary Document, unless permission is granted by the sponsor or it is published elsewhere between the time of the PBAC meeting and these PBAC-derived publications.

The ESC considered that the proposed managed entry scheme should be built around the ongoing phase III clinical trial (KN-006) with its stated co-primary endpoints of progression-free survival and overall survival.

The PBAC considered that the MES for pembrolizumab should be guided by the following.

- The initial price of pembrolizumab for PBS listing would be determined on the basis of the current cost per patient to the PBS of ipilimumab at its effective price. Rather than a direct price reduction, this would be achieved by setting the RSA expenditure caps for pembrolizumab with reference to the average cost of ipilimumab per patient using appropriate historical PBS dispensing data, and the revised utilisation estimates based on current ipilimumab utilisation via the PBS. These data indicated that approximately patients have commenced ipilimumab each year, with an average of induction doses per patient, with approximately % of these patients having undergone reinduction therapy with ipilimumab. The annual percentage increases in utilisation after the first year would be calculated as described in the submission (see table after paragraph 6.65 above). Any annual pembrolizumab expenditure beyond these caps should be rebated % to the Commonwealth to generate the reduced effective price to apply from initial listing until such time as it might change at the end of the MES.

- The review of new evidence should be provided as soon as possible (and expected to be within two years) after maximal follow-up of the KN-006 trial, noting that the final analysis of overall survival for this trial is expected to report in the second quarter of 2016.

- The clinical evaluation for KN-006 should formally report both progression free survival (PFS) and overall survival (OS) using the standard graphics of Kaplan-Meier curves, and with standard reporting of results.

- The economic evaluation based on KN-006 should directly use the Kaplan-Meier curves observed based on individual patient data from the trial to estimate incremental PFS and incremental OS up to the median duration of follow-up across the two arms compared in the clinical evaluation, and then apply extrapolation modelling for both arms for PFS and OS curves from this time point, i.e. no statistical adjustments should be used to account for differential use of post-progression therapies.

Figure 2: PBAC’s consideration of pembrolizumab.

The PBAC noted that, following lodgement of the submission on 5 November 2014, an extraordinary amount of important additional information was provided throughout the process of evaluation, including:

- 24 November 2014: trial data from KN-002 provided by the sponsor (20 slides)
- 28 January 2015: revised model and revised managed entry scheme (MES) proposal with the PSCR (16 pages)
- 13 February 2015 (after the ESC meeting): early results of KN-006 provided by the sponsor (38 pages) (KN-006 = randomised trial data directly comparing pembrolizumab with ipilimumab in ipilimumab naïve patients)
- 17 February 2015: TGA delegate’s overview provided by the sponsor (96 pages)
- 25 February 2015: Attachment and PES Addendum to the ESC Advice to comment on the additional post-submission information (20 pages)
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- 6 March 2015: additional information provided by the sponsor on proposed subsidised access to pembrolizumab for ipilimumab refractory patients via a funding arrangement from the sponsor (2 pages)
been established. The PBAC also noted the higher rate of adverse events with combination therapy compared with dabrafenib mesylate monotherapy.

In November 2014, the PBAC considered a resubmission for trametinib dimethyl sulphonide that included a Managed Entry Scheme (MES) proposal. A MES provides a mechanism to address the uncertainty over the size of the additional clinical benefit of new medicine while providing early access to those patients for whom there is a high clinical need.

The PBAC recommended the listing of trametinib dimethyl sulphonide for use in combination with dabrafenib mesylate for the treatment of patients with BRAF V600 mutation positive stage III or stage IV malignant melanoma. Trametinib dimethyl sulphonide was listed on the PBS under a MES on 1 August 2015.

Information about the benefits of trametinib dimethyl sulphonide in clinical practice will be collected, analysed and presented to the PBAC for consideration in the near future. Prescribers and patients must be aware that trametinib dimethyl sulphonide does not prove as beneficial in clinical practice as appeared in the clinical data presented to the PBAC, it may subsequently have its restriction modified or be removed from the PBS by the Commonwealth, or at the request of the sponsor.

Pembrolizumab

The PBAC considered a submission to list pembrolizumab on the PBS for the treatment of patients with stage IIIC or stage IV melanoma in March 2015. The submission was considered under the TGA/PBAC parallel process; the main indication sought was for first-line use by ipilimumab naïve patients.

The PBAC's consideration of this submission is discussed in Figure 2.

The PBAC recommended the listing of pembrolizumab as for use as monotherapy by patients with stage III or stage IV melanoma, with an initial risk share arrangement to achieve the same cost per patient to the PBS as is currently the case for ipilimumab, to thus give a reduced effective price of pembrolizumab.

The PBAC recommended that the listing should be limited to patients who have not been exposed to ipilimumab, noting that the sponsor has undertaken to subsidise ongoing access to pembrolizumab for patients who are refractory to ipilimumab.

The PBAC supported the sponsor’s request that, for patients with a BRAF mutation, the PBS listing of pembrolizumab should follow progression after treatment with dabrafenib mesylate (combined with trametinib dimethyl sulphonide after trametinib dimethyl sulphonide is listed).

Pembrolizumab was listed on the PBS under a MES on 1 September 2015.

Nivolumab

The PBAC considered a submission to list nivolumab on the PBS for use by patients with stage III or stage IV melanoma in July 2015. The PBAC rejected the submission because it failed to include a comparison with pembrolizumab.

Reimbursement (England)

The medicine reimbursement program in England, including the role of NICE, is summarised in Table 4.

In March 2014, the Medicines & Healthcare products Regulatory Agency (MHRA) announced it was launching an Early Access to Medicines Scheme (EAMS), saying it would allow earlier access to potentially lifesaving medicines for patients with severe or life-threatening conditions.

For a new medicine to qualify for the EAMS, it must be granted a promising innovative medicine designation based on early (phase I and/or II) clinical data and satisfy additional criteria including the severity of the condition the medicine is intended to treat and the level of improvement over previously authorised treatments.

The MHRA has approved two medicines for melanoma under the EAMS: pembrolizumab and nivolumab.

NICE has assessed the following new treatments for patients with melanoma:

- Vemurafenib—recommended as an option for treating BRAF V600 mutation positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme (December 2012).
• Ipilimumab—recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme (July 2014).

• Dabrafenib mesylate—recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation positive melanoma only if the company provides dabrafenib mesylate with the discount agreed in the patient access scheme. (October 2014).

• Pembrolizumab—recommended as an option for treating advanced (unresectable or metastatic) melanoma in adults only after the disease has progressed with ipilimumab and, for BRAF V600 mutation positive disease, a BRAF or MEK inhibitor and when the company provides pembrolizumab with the discount agreed in the patient access scheme (October 2015). Because pembrolizumab was made available in the NHS through the early access to medicines scheme, NHS England has indicated that this guidance will be implemented 30 days after final publication. In November 2015 pembrolizumab was recommended as an option for the treatment of adults with advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, only when the company provides pembrolizumab with the discount agreed in the patient access scheme.

• Trametinib dimethyl sulphoxide—recommended for use in combination with dabrafenib mesylate for the treatment of patients with advanced unresectable or metastatic BRAF V600 mutation positive melanoma in June 2016.

• Nivolumab—recommended for use for the treatment of patients with advanced, unresectable or metastatic melanoma in February 2016.

Table 5 summarises the current reimbursement status of the new treatments for patients with melanoma.

Discussion

Significant advances have occurred in the drug treatment of patients with metastatic melanoma since 2010. The development of the BRAF and MEK inhibitors, and immune checkpoint inhibitors, offer unprecedented clinical benefits to patients with advanced disease. Important advantages of these novel drugs are their ability to treat sites of disease previously viewed as refractory to systemic therapy, and manageable toxicity profiles. As a result, there has been accelerated regulatory approval of some of these agents. However, all of these treatments are high-cost, and the reimbursement process fundamentally drives access to them.

Timely access to at least one agent in each class of drug is critical in New Zealand, Australia and England, where metastatic melanoma is a major public health concern. When confronted by the evidence surrounding the funding process in the three countries, the differences are stark. The reimbursement/HTA agencies in Australia and England, recognising the unmet need of melanoma patients and acknowledging the importance of equitable geographical access, have taken innovative and extraordinary measures to make at least one drug from each novel class available in a timely manner. In contrast, New Zealand’s agency, PHARMAC, has rejected multiple applications to fund any of these drugs over a four-year period, and there are no signs to indicate that any of them will be listed in the New Zealand Pharmaceutical Schedule anytime soon. It is difficult to understand, let alone accept, such inertia with the melanoma statistics of this nation.

The recommendation by a technical advisory committee (PTAC) that PHARMAC run a competitive tender to fund one of ipilimumab, vemurafenib and dabrafenib mesylate, is unusual; we are not aware of the PBAC or any of the NICE Appraisal Committees having provided similar tactical advice to their corresponding bureaucracies. Furthermore, the PTAC recommendation that PHARMAC run a competitive tender to fund medicines that have different modes of action undermines the basic science and makes one start to question whether the primary focus of the Committee is science (pharmacology) or finance (money).
These new medicines are expensive but they are also effective. We are not calling for their immediate reimbursement without a thorough and fair assessment of their value (eg, cost effectiveness). The PBAC rejected most of the initial submissions for these medicines. Nonetheless, we urge the Government and/or PHARMAC to find solutions to the current unacceptable access stalemate. New Zealanders with melanoma deserve better than this; we suspect that patients are suffering to the point of dying due as a result. It is nigh on impossible to obtain empirical data to prove this; whilst it is (somewhat) easy for PHARMAC to calculate how much money it has saved, it is much harder to determine how many lives have been lost as a consequence.

New Zealand should not be in the unenviable position whereby it has the highest incidence of a fatal disease yet it is the last country in the Western world to fund effective treatments for it.

We note the recent PHARMAC report on access to new cancer medicines with the associated claim that New Zealanders are getting access to the best cancer medicines available.\(^{50}\) The findings from this study are

**Table 5:** Summary of the reimbursement status of the new treatments for patients with melanoma.

<table>
<thead>
<tr>
<th>Medicine (generic name)</th>
<th>Ipilimumab</th>
<th>Vemurafenib</th>
<th>Dabrafenib mesylate</th>
<th>Trametinib dimethyl sulphoxide</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
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<tr>
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<td>No outcome</td>
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<tr>
<td>Date of listing/implementation</td>
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<td>Not listed</td>
<td>Not listed</td>
<td>Not listed</td>
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<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>
in stark contrast to other studies that have found New Zealanders have poorer access to new medicines in general.\textsuperscript{51,52} Notwithstanding our concerns about many aspects of the PHARMAC analysis, it has scant reference to the new medicines for melanoma.

We describe a number of examples of the momentum in Australia and England to reimburse new systemic treatments for patients with metastatic melanoma in a timely manner. Both countries have introduced schemes that allow early access to promising therapies for patients with life-threatening diseases, while managing the risks associated with evolving clinical trial data and real-world experience. A central principle of the MES in Australia is the ongoing evaluation of promising new medicines with the commitment to providing patients with the most efficacious and safest treatments at a given time; in other words, the reimbursement process will attempt to keep in step with the latest evidence. It is our strong view that New Zealand should look to adopt a similar scheme.

Another example of the commitment to a high standard of care for melanoma patients is the harmonization of the processes for the reimbursement of a medicine and its corresponding diagnostic test, demonstrated by Australia’s PBAC and MSAC assessment of dabrafenib mesylate and BRAF mutation analysis. To our knowledge, no such procedure exists in New Zealand and is a further weakness that may lead to sub-standard and inequitable care for melanoma patients.

What is/are the causes of the inertia?

- PHARMAC is yet to receive funding applications for these medicines from their respective sponsors. This seems unlikely as submissions for most of the new medicines have already been considered by PTAC. PHARMAC is yet to publish all of the funding applications that were considered by the PTAC in August and November 2015.
- There is no funding. The listing of these medicines in the New Zealand Pharmaceutical Schedule will come at a cost to the fixed PHARMAC budget. It is unclear if PHARMAC has the budget to list some/all of these medicines. Likewise, it is unclear if PHARMAC has asked the Government for extra funds if the current PHARMAC budget precludes their listing.
- The clinical benefits of the new treatments are lacking or are uncertain. Notwithstanding the concerns of the PTAC and others about the benefits and harms of the new treatments over the long term, this has not prevented their reimbursement in Australia and England (and elsewhere). Their inclusion in authoritative clinical guidelines suggests that other experts in the field are of the view that their clinical benefits outweigh their risks.
- Poor access to co-dependent technologies; whilst this may be an issue for dabrafenib mesylate and vemurafenib, it isn’t for ipilimumab, trametinib dimethyl sulphoxide and pembrolizumab.
- Proposed unit prices are ‘unacceptable’ to PTAC/PHARMAC. This is an issue but we have limited information to evaluate this. Other HTA agencies have also expressed concerns about their high unit costs but this has not prevented their reimbursement.

In the light of the above, we offer the following recommendations to all stakeholders:

- PHARMAC invite/encourage all relevant sponsors to lodge funding applications, regardless of whether they have been approved by Medsafe
- Medsafe consider expediting its assessment/approval process for certain new medicines
- PTAC uphold the underlying science in funding applications
- Government explore options for the subsidized access to necessary co-dependent technologies. This may well be an additional role for PHARMAC.
- PHARMAC consider funding some of these new medicines before their registration by Medsafe. While there is no legislative impediment to this, there may be a budgetary one.
- PHARMAC ask the Government for additional monies to fund some/all of these new medicines if PHARMAC’s fixed budget for the current financial year has been exhausted/fully committed.
• PHARMAC consider the adoption of new access models such as the new MES in Australia and the patient access scheme in England
• The sponsors of the medicines concerned prepare and submit funding applications that include realistic pricing/funding proposals. PHARMAC should consider these applications as soon as possible.

PHARMAC has done an excellent job over many years in containing pharmaceutical expenditure in New Zealand. The agency has been very successful in focusing the public discussion on the country's medicine reimbursement program to fiscal matters. Discussions on the value of new medicines and the health forgone have gained little attention. It is high time to shift the focus of the discussion from cost to value. Likewise, it is time to shift the current mindset of PHARMAC from being a defender of the public purse to a pragmatic problem solver.

Authors' footnote 19 July 2016:
This manuscript was submitted for publication on 16 December 2015 and accepted for publication on 4 May 2016. We note the subsequent events:
• On 28 April 2016, Medsafe approved nivolumab for use as monotherapy for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma and in combination with ipilimumab for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).
• On 4 May 2016, PHARMAC announced that it proposed to list nivolumab on the New Zealand Pharmaceutical Schedule, as monotherapy for advanced melanoma patients.
• On 9 May 2016, PHARMAC published a CaTSoP minute on nivolumab. The Subcommittee considered an application from Bristol-Myers Squibb on 22 April 2016 for the listing of nivolumab as monotherapy and in combination with ipilimumab for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma. CaTSoP recommended the listing of nivolumab for the former patient population (medium/high priority) and deferred it for the latter patient population.
• On 18 May 2016, PHARMAC published a PTAC minute on nivolumab. On 5-6 May 2016, the PTAC considered a funding application for nivolumab for use and monotherapy and in combination with ipilimumab. The PTAC recommended the listing of nivolumab as monotherapy (medium priority) but rejected its listing for use in combination.
• On 9 June 2016, following a consultation period, PHARMAC announced the decision to fund nivolumab from 1 July 2016, for patients meeting the special authority criteria.
• The proposed special authority criteria were amended, including provision for nivolumab to be combined with ipilimumab (noting that ipilimumab remains unfunded).
• On 29 June 2016, PHARMAC commenced consultation on a proposal to fund pembrolizumab from 1 September 2016
• PHARMAC has confirmed that funding applications for pembrolizumab, BRAF and MEK inhibitors remain under consideration. PHARMAC is yet to publish details on the funding applications that were considered by the PTAC in February and May 2016. It is unclear if PHARMAC has received additional funding applications for these medicines.

The decision to fund nivolumab and the consultation on the funding of pembrolizumab must be viewed as significant advances, but does not influence our concluding remarks.
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44. PHARMAC. Available at http://www.pharmac.health.nz [Accessed 9 December 2015].


