Clinical review of pembrolizumab (Keytruda)

A summary of advice to PHARMAC and the application process

Executive Summary

- Pembrolizumab (Keytruda) is a treatment for patients with advanced melanoma. It is a new way of treating cancer and therefore holds promise. As a very expensive new treatment PHARMAC needs to know whether that promise will be realised.

- PHARMAC has rapidly assessed the application for providing public funding, and received advice from experts in the field of cancer treatment and data interpretation.

- According to current data most people who receive pembrolizumab for malignant melanoma will not see a response in their tumours. Of those people that do get a response, it is not clear at this time whether pembrolizumab will help them live longer.

- The data is not conclusive, but does signal a level of effectiveness in a cancer that has previously had very few treatment options. Our expert advisors recommend pembrolizumab as an option for funding, but not ahead of other medicine funding options that offer a better balance of evidence and price.

- In order to address these issues PHARMAC will be working with the pharmaceutical company on the future data availability as well as potential commercial solutions.

What is PHARMAC looking at?

PHARMAC is assessing an application to list pembrolizumab (Keytruda) on the Pharmaceutical Schedule. This is a new treatment for melanoma for which the clinical evidence is still emerging. The application from Merck Sharp & Dohme seeks funding for pembrolizumab for people with advanced melanoma (metastatic or unresectable Stage 3 and 4 melanoma). Medsafe, New Zealand’s medicines regulator, approved pembrolizumab for this use in September 2015, and there are other clinical trials underway testing it in many other types of cancer.

There has been strong public interest in this medicine; however, there is a gap between the public’s perception of the benefits offered by pembrolizumab and the measured benefits seen in the clinical trials to date. While it is not unusual for a public relations campaign to hope to influence PHARMAC’s funding decisions, we follow a robust process to ensure that we are fair to all patients waiting for treatments to be considered and that we make good decisions on the next best spend of the health dollar to the benefit of all New Zealanders.

Who do we get our clinical advice from?

In our funding assessments we first seek advice from the Pharmacology and Therapeutics Advisory Committee (PTAC), which is made up of 12 senior doctors and pharmacologists who are experts in reviewing and interpreting complex clinical data on pharmaceuticals. We sought advice on pembrolizumab from both PTAC and its Cancer Treatments Subcommittee (CaTSoP), a specialist committee made up of nine independent cancer specialists with expertise in treating people with cancers, including melanoma. Obtaining objective advice from clinical experts provides assurance to New Zealanders that we have carefully considered the relevant evidence for how well a medicine works, for which patients and in which illnesses.

What benefits were shown in the trials?

The trials show pembrolizumab may have some early benefits for some people and some risks for some people. In some people treated with pembrolizumab, tumours shrank or disappeared, and there was a delay in the tumour returning. In most of those people whose tumours did respond to treatment, their tumour response was maintained until the time of data analysis.

In the main trial (Keynote-006), the majority of people treated with pembrolizumab either had no change in tumour size or their tumours grew. For one in three people, tumours shrunk or disappeared completely and this response was maintained until the time of data analysis when half of the patients had been on the trial for 8 months or less.
No clinical trial has yet shown that pembrolizumab increases the length of life for melanoma patients compared with other new melanoma treatments or standard chemotherapy.

Are there risks?
The trials showed pembrolizumab has some side-effects, with around 1 in 10 people experiencing a severe side effect, although the clinical experts thought these side effects were manageable. Pembrolizumab appeared to be less toxic than ipilimumab, another new melanoma treatment that the Committees had previously reviewed.

What did the clinical committees recommend?
The clinical experts thought that pembrolizumab has benefits for some people, and there is a lack of currently funded effective treatments for melanoma. They recommended pembrolizumab be funded, and gave their recommendation a low priority. This is because of the current uncertainty about the magnitude and long-term durability of any benefit, together with the extremely high cost.

Why did they reach this conclusion?
The Committees looked at published and unpublished results of the clinical trials of pembrolizumab; Keynote-001, Keynote-002, and Keynote-006 (refer to appendix – About clinical trials). The trials looked at aspects of the use of pembrolizumab including: what the best dosing is, its effectiveness on early markers of effectiveness (surrogate endpoints), and its safety. Usually with a medicine seeking funding, we would expect to see firm evidence on what the optimal dose is, and long-term data on safety and efficacy from Phase 3 trials. This type of evidence is currently limited for pembrolizumab.

All of the clinical trials for pembrolizumab have design and/or conduct issues that make it difficult to say with any certainty how great the benefit, nor how long-lasting it would be for patients.

What else did the committees take into account?
As well as the clinical evidence and risks and benefits for pembrolizumab, the Committees took into account the high incidence of melanoma in New Zealand, the current lack of effective funded treatments for advanced melanoma in New Zealand, and the cost of pembrolizumab.

What does the recommendation mean?
Clinical advice on the benefits and risks of pharmaceuticals is one of the things PHARMAC takes into account when it makes its funding decisions. Generally speaking, pharmaceuticals with a low priority are less likely to be funded than those with a medium or high priority. The next step is for PHARMAC to work with the pharmaceutical company to see if the issues can be resolved through further data provision or through commercial means.

Why is this different to other countries?
In New Zealand very clear choices must be made around the use of the defined funding for medicines. PHARMAC is particularly careful to select the medicines offering the best overall health outcomes. We are aware that funding a promising new treatment which may not ultimately live up to that promise means that other New Zealanders miss out on access to treatments that are well proven.

What's needed for PHARMAC to fund pembrolizumab?
Pembrolizumab is an expensive medicine. For PHARMAC to justify an investment of this size, we'd need to see more certainty of benefit in the evidence, and more reliable evidence on the best use of pembrolizumab. We’re willing to consider how we might work with the supplier to develop the evidence base and/or set a more appropriate price given the current evidence base.

We currently consider that other medicines offer better, and more certain, value than pembrolizumab in terms of delivering better health outcomes for all New Zealanders.
Appendix - About clinical trials

In order to fully understand the benefits and risks of a new medicine a pharmaceutical company must undertake a range of clinical trials as part of its clinical development programme for a new medicine. Clinical development programmes usually comprise four phases, with each phase conducted consecutively using the information collected in the previous phase. These phases, their primary purpose and typical clinical trial designs are outlined in the table below:

<table>
<thead>
<tr>
<th>Clinical Development Phase</th>
<th>Primary purpose</th>
<th>Typical clinical trial design</th>
<th>Typical number of trial participants</th>
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<tbody>
<tr>
<td>Phase I (1)</td>
<td>To test for preliminary safety and establish the optimal dose of the new medicine</td>
<td>Small numbers of healthy volunteers or sometimes patients. Initially low doses of the new medicine are given with doses increased overtime.</td>
<td>20-100</td>
</tr>
<tr>
<td>Phase II (2)</td>
<td>To test for safety and preliminary effectiveness of the new medicine in patients</td>
<td>All patients given the new medicine at the optimal dose.</td>
<td>100-300</td>
</tr>
<tr>
<td>Phase III (3)</td>
<td>To establish the safety and efficacy of the new medicine compared with the current medicine normally used in patients. It is typically expected that there be at least two successful Phase III trials conducted.</td>
<td>Half of the patients are given the new medicine (investigational group) at the optimal dose, with the other half given placebo and/or the current standard medicine (comparator or control group). Patients are randomly assigned to one of the two treatment arms. They are commonly known as Randomised controlled trials (RCTs). Sometimes these trials are ‘blinded’ (meaning that neither the patient nor their doctor knows what medicine each patient is getting), or ‘open-label’ (meaning that both the patient and their doctor know what treatment they are getting). Blinded trials are preferred as they avoid bias in assessing outcomes. Spontaneous reporting of safety issued by doctors when they use the treatment in any of their patients</td>
<td>300-3000 or more depending on the disease</td>
</tr>
<tr>
<td>Phase IV (4)</td>
<td>To monitor for safety concerns in the public after the new medicine has been approved by the regulator for sale</td>
<td>Spontaneous reporting of safety issued by doctors when they use the treatment in any of their patients</td>
<td>NA</td>
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The reliability of the results obtained from clinical trials is highly dependent on their design and conduct. Various aspects of clinical trial design and conduct can have a substantial negative effect on the reliability and relevance of clinical trial results, for example:

- short follow-up of patients
- use of early (so called ‘surrogate’) measures of benefit
- multiple analyses of the same trial
- cross over of patients from the control group to the investigational group
- enrolling patients that are different to those that will be treated in normal practice
- using different doses of the medicine than will be used in practice.

**Pembrolizumab clinical trials**

The current clinical trial evidence for pembrolizumab in advanced melanoma comprises one Phase I trial, one open-label Phase II/III trial and one open-label Phase III trial:

- **Keynote-001** was a Phase I trial that included both advanced lung cancer and melanoma patients and looked at various doses of pembrolizumab, there was no comparator treatment or control group in this study.

- **Keynote-002** was an open-label Phase II/III trial that compared two different doses of pembrolizumab treatment with standard chemotherapy treatment (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or temozolomide) in patients with advanced melanoma whose disease had progressed following prior treatment with ipilimumab. This trial enrolled patients with advanced melanoma who had previously been treated with ipilimumab and/or a BRAF inhibitor.

- **Keynote-006** was an open-label randomised controlled Phase III trial for pembrolizumab, it compared two different doses of pembrolizumab with ipilimumab treatment in patients with advanced melanoma. This trial enrolled patients with advanced melanoma who had not received any previous treatment or who had previously been treated with ipilimumab and/or a BRAF inhibitor.