Pharmaceutical Benefits Advisory Committee (PBAC)

PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types

Background to invitation for submissions
May 2018

Submissions should be made in writing by 5 pm AEST 29 June 2018,

Please use the template provided.

Submissions should be sent to pbac@health.gov.au.

The outcomes of the PBAC's considerations will be published through the PBS website.

1 Introduction

1.1 The Hon. Minister Hunt, Minister for Health requested the Pharmaceutical Benefits Advisory Committee (PBAC) to provide advice for consideration of options for listing PD-1 and PD-L1 checkpoint inhibitors for the treatment of multiple cancer indications on the PBS.

2 Background

2.1 Cancer occurs when cells grow in an uncontrolled way. These abnormal cells can damage or invade the surrounding tissues, or spread to other parts of the body, causing further damage.

2.2 There are many different types of cancer, and usually they are named for the organ or cell type of the primary cancer. For example, bladder cancer starts in the bladder, prostate cancer starts in the prostate, lung cancer starts in the lung[i].

2.3 Checkpoint inhibitors medicines are a type of immunotherapy. Checkpoint inhibitors block certain proteins made by some types of immune system cells, such as T cells and some cancers. When these proteins are blocked, the immune system can attack the cancer. Examples of checkpoint inhibitor medicines include nivolumab (Opdivo®) and pembrolizumab (Keytruda®) which block the PD-1 protein and atezolizumab (Tecentriq®), avelumab (Bavencio®), and durvalumab (Imfinzi®) which block the PD-L1 protein.

2.4 Checkpoint inhibitors have been shown to produce good responses in some cancers but not in all cancers and not in all patients. Testing for biomarkers including PD-L1 and TMB (tumour mutational burden) may be useful in some cancers but the results are variable and research is still being undertaken to identify and validate accurate biomarkers. Clinical studies of checkpoint inhibitors are continuing in a range of different cancers. In some studies, the checkpoint inhibitor is used as monotherapy, and in others combined with anti-cancer

therapy such as chemotherapy or radiotherapy. Importantly, checkpoint inhibitor therapy has been shown to be ineffective in some types of cancer and in some other cancer types, to be less effective than standard anti-cancer therapies.

2.5 The Pharmaceutical Benefits Scheme (PBS) currently provides subsidised access to checkpoint inhibitors for certain patients with classical Hodgkin lymphoma, lung cancer, kidney cancer and melanoma. Subsidy is available for people whose cancer is advanced or metastatic or has relapsed following other treatments. It is expected that PBS subsidy may soon be extended to provide access to certain patients with head and neck cancer[ii]. In these types of cancer, evidence from clinical trials has demonstrated effectiveness and benefit of checkpoint inhibitors compared to prior standard of care therapy.

2.6 Applications for PBS subsidy of PD-1 and PD-L1 checkpoint inhibitors for certain patients with Merkel Cell Cancer and bladder cancer are currently being considered by the Pharmaceutical Benefits Advisory Committee (PBAC). Also under consideration are applications to expand the patient groups eligible for subsidised access to PD-1 and PD-L1 checkpoint inhibitors for melanoma and lung cancer, and to allow combined use of a checkpoint inhibitor and ipilimumab (Yervoy®) in some melanoma and kidney cancer patients[iii].

2.7 The PBAC is aware that the Department has received two preliminary proposals for multi-tumour approaches. One proposal makes no changes to the PBAC process. The second proposal sees the PBAC determine an average price for this class of medicines that would apply to a pre-specified range of indications for a pre-specified period of time. Medicines in the class would then be added to the PBS as soon as practical following registration. The proposal does not detail how the PBAC would determine the average price.

2.8 Both proposals suggest price-volume arrangements to manage the overall cost to Government. Pre-specifying a price volume arrangement has the potential to simplify Government processes after a positive PBAC recommendation, but requires agreement on a range of matters that are usually considered within the PBAC evaluation process.

2.9 It has also been proposed by some stakeholders that a multi-tumour approach should allow subsidised access to PD-1 and PD-L1 inhibitors to patients with rarer cancers where usual evidence of effectiveness may take a long time to gather.

3 Health Technology Assessment (HTA) and the Pharmaceutical Benefits Advisory Committee (PBAC)

3.1 The HTA process plays a vital role in ensuring the Australian Governments' objective of delivering a safe, effective and efficient health care system. The goal of Australian Government HTA processes is to maximise beneficial health outcomes to the Australian population within the overall funds available, whilst being cognisant of the other important goals of the health system.[iv]

3.2 The purpose of Australian Government HTA processes is to provide policy-makers, funders, health professionals and health consumers with the necessary information to understand the benefits and comparative value of all health technologies and procedures.

3.3 The Australian Government HTA processes aim to use the best available evidence and efficient methods to inform robust decisions about the subsidised use of health technologies. This contributes to a sustainable health system through informing evidence based decisions about the subsidised use of health technologies.[v] These health technologies include pharmaceuticals (including vaccines), diagnostic tests, medical devices, surgically implanted prostheses, medical procedures and public health interventions[vi].

3.4 The PBAC is an independent expert advisory committee with expertise in clinical and health economic and consumer matters. The PBAC is established under the *National Health Act 1953.* The Minister cannot subsidise a medicine through the PBS without a recommendation from the PBAC.

3.5 Australia has one of the fastest HTA processes for reimbursement decisions for medicines in the world, comparing favourably with other Organisation for Economic Co-operation and Development (OECD) countries in terms of the time from submission to the first reimbursement decision and the percentage of medicines recommended for reimbursement in the same year as the medicine's regulatory approval.[vii]

3.6 When considering a medicine for subsidy through the PBS, the PBAC is required by law to give consideration to the effectiveness and cost of the medicine (cost-effectiveness), including by comparing the effectiveness and cost with that of alternative treatments. The PBAC cannot recommend a medicine for subsidy unless it is satisfied that it is cost-effective[viii].

3.7 Where the PBAC is of the view that a medicine should be made available on the PBS, but only for certain uses (circumstances), the Committee species those uses.

3.8 The cost-effectiveness of the same medicine used to treat different cancer types can vary significantly. This is because of a range of factors including: differences in the natural history of different cancers, differences in patient response to the same medicine and differences in the treatments already available for different cancers. These factors mean that the PBAC usually has to evaluate each medicine separately for each indication or cancer type.

3.9 The PBAC has already noted that while it is likely that PD-1 and PD-L1 checkpoint inhibitors will be useful for treating a range of cancers, the limited trial results submitted to the Committee to date (see Table 1) suggest that treatment responses are highly variable across different types of cancers, different ages, different patient populations, and different comparators. Consequently, the relative effectiveness and safety of the same medicine will vary and the medicine will not have the same value for money in all cancers. There is also the risk that patients will be exposed to ineffective or harmful therapy[ix], compared with standard of care cancer treatments (chemotherapy, targeted therapy and radiation).

3.10 Additionally, there is an inconsistent and highly variable relationship between the presence of PDL1 tumour expression and response to immunotherapy for different cancer types. It is not possible to use PDL1 expression as a reliable way of predicting which cancer patients will respond to immunotherapy. This highlights the complexities for identifying optimal target populations and then predicting their probable responses to treatment.

3.11 Moreover, in most cases, results from trials are still early in terms of estimating overall and comparative benefits, factors of key importance for PBS reimbursement decision-making

under the *National Health Act 1953*. The early information that is available from clinical studies can be limited to tumour response or progression-free survival data. Although these measures are both important, they do not always translate to an improvement in overall patient survival, or length of life, or to an improvement in quality of life. The available information for PD-1 and PD-L1 inhibitors also suggests that often only a small fraction of patients will experience a long-term durable response.[x]

3.12 The reliance on data from early studies can be misleading. The potential benefits may be exaggerated and consequently be found to be smaller when longer term data becomes available. Safety problems may not yet be revealed which would have been observed through longer term pathways.[xi] The converse may also be true.

Summary of data available to PBAC at the time it first recommended/deferred[1] subsidy

	Melanoma	Lung First Line	Lung Second Line	Kidney	Hodgkin disease	Head and Neck Cancer
Medicine	Pembrolizumab[2]	Pembrolizumab[1]	Nivolumab[1,3]	Nivolumab	Pembrolizumab	Nivolumab
PSD	March 2015	November 2017	November 2016	March 2017	July 2017	November 2017[4]
Age cohort studied	Mean 60 years	Mean 64 years	Mean 62 years	Mean 60 years	Mean 40 years	Mean 59 years
Comparator	Ipilimumab	Platinum based doublet chemotherapy	Docetaxel (squamous) Pemetrexed (non-squamous)	Everolimus	Brentuximab vedotin	Standard of Care: Paclitaxel, docetaxel, methotrexate or capecitabine
Outcome vs comparator	Final OS data not available Early data: For every 100 patients treated, 10-13 more will be alive at 6 months.	Final OS data not available Early data: For every 100 patients treated, 15 more will be alive at 1 year.	For every 100 patients treated, 15 - 16 more will be alive at 18 months compared to docetaxel. Comparison versus pemetrexed not available.	For every 100 patients treated, 9 more will be alive at 1 year.	Similar clinical benefit to brentuximab vedotin.	Not available for publication.
PDL1 marker	No	Yes ≥ 50%	No	No	No	No

Data extracted from Public Summary Documents (PSD) available at www.pbs.gov.au; OS = overall survival.

[1] For the two deferred submissions (nivolumab lung November 2016, and pembrolizumab lung March 2018) the outstanding issues were not related to the clinical data
[2] Nivolumab was recommended for subsidy on a cost-minimisation basis with pembrolizumab. Results not separately reported here.
[3] Atezolizumab was recommended for subsidy of a cost-minimisation basis with nivolumab. Results not separately reported here.
[4] Taken from November 2017 PSD when nivolumab was rejected by the PBAC for this indication. PSD for March 2018 PBAC consideration not published.

4 August 2018 PBAC special meeting

4.1 The purpose of the August 2018 PBAC special meeting is to allow the Committee to consider potential future options for the evaluation and consideration of PD-1 and PD-L1 checkpoint inhibitors for multiple cancer types.

4.2 In its considerations the Committee will take account of the tensions existing between the demands for adapting the reimbursement pathways for multiple tumour medicines, while balancing the uncertainties in the clinical and/or economic evidence base.

4.3 The Committee will also consider patient and community interests including timely access to new medicines, unmet clinical need and the principles of equitable access and affordability for improved health outcomes across all disease groups.

4.4 Any options put to the Minister will also need to meet the core objectives of the Australian Government HTA framework and take into account the role of the Therapeutic Goods Administration in approving medicines for marketing in Australia, whilst allowing the PBAC to meet its statutory obligations. Those obligations are set out in Section 101 of the *National Health Act 1953.* Further information on current PBAC evidentiary requirements can be found in the Guidelines for Submissions to the PBAC, available at https://pbac.pbs.gov.au/.

4.5 The PBAC reimbursement decision process works on a 17-week cycle (85 business days) from submission to PBAC consideration and decision. Any process designed to fast track / accelerate access will need to be integrated within the existing regulatory and reimbursement framework for medicines and will necessarily require additional resources, timeline flexibilities and new criteria for engagement with all stakeholders.

4.6 These investments would require justification on the basis of certain medicines / clinical interventions being deemed to address a high unmet need, balanced with cost effectiveness and affordability.

4.7 The success of any approach that is adopted will also depend on the willingness of sponsors to accept prices and listing conditions that reflect the PBAC's view of the available evidence.

4.8 Options that require changes to the regulatory framework in which the PBAC operates will need to be considered by Government and are beyond the scope of what PBAC can provide advice on through its August 2018 special meeting.

4.9 The Committee is inviting submissions from interested parties ahead of the August meeting.

4.10 The following questions are designed to provide a framework for submissions to the PBAC on this matter and for the PBAC's considerations of those submissions. These questions are not intended to be exhaustive.

Broad questions for consideration in preparing submissions to the PBAC

1. What do you/your organisation see as the potential advantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings?

2. What do you/your organisation see as the potential disadvantages of the PBAC considering the PD-1 and PD-L1 checkpoint inhibitors for multi-tumour listings?

3. What is urgent unmet clinical need? How should it be established? For which patient groups?

4. What is the minimum level of evidence of effectiveness that you/your organisation think should be required before a PD-1 and PD-L1 checkpoint inhibitors is considered for subsidy for a particular kind of cancer? Why?

5. Do you/your organisation think it is possible for the PBAC to be able extrapolate, or apply, the evidence of effectiveness of a checkpoint inhibitor in one kind of cancer to another kind of cancer, or from late stage cancer to early stage cancer? Why? How?

6. Do you/your organisation think it is possible for PBAC to satisfy itself that treatment with a PD-1 or PD-L1 checkpoint inhibitor is cost-effective without an economic model that is specific to that kind of cancer? How?
    - Is it possible to group different cancer types together based on particular characteristics that are similar, and construct a single model for the group?
    - Are other approaches to establishing cost-effectiveness across cancer types possible? What are those approaches and how would they operate?

7. What do you/your organisation think is a reasonable subsidy price for Government to pay for a PD-1 or PD-L1 medicines for cancer types where the benefit is potentially very modest?

8. Do you/your organisation think PD-1 and PD-L1 medicines should be made available to all patients whose cancers display a particular biomarker? Why? Which biomarker?

9. Do you/your organisation think it is appropriate for the PBAC to extrapolate the evidence from one PD-1 or PD-L1 checkpoint inhibitor to other medicines in the same class(es). This could provide patients with more choice and give Government the opportunity to negotiate better subsidy prices by utilising the competition between sponsors of medicines.

10. Do you/your organisation think that different evidentiary requirements are appropriate for rare cancers? How do you think cost-effectiveness should be established in this case?
11. Do you/your organisation think PBAC should set aside one of its meetings each year to consider only PD-1 or PD-L1 inhibitors for cancer? (This would mean no other submissions for other medicines, including other cancer medicines, or other diseases would be considered at that meeting.)

12. If limited evidence is available at the time of subsidy of a PD-1 or PD-L1 inhibitor for a type of cancer , what do you/your organisation think should happen afterwards?
    - Should sponsors be required to collect more evidence?
    - What should happen if the new evidence shows the medicine is less effective or has greater safety risks than expected?
    - Should the medicine continue to be subsidised but at a price commensurate with its benefit? Should the sponsor be compelled to continue to make the medicine available even if it thinks the price is too low?

13. **(For industry/clinical groups)** Clinical study information: (Please use the template provided for this information.)
    - In what indications has your organisation completed clinical trials with a PD-1 and PDL1 inhibitor? Please include both positive and negative studies.
    - In what indications is your organisation currently conducting or planning to conduct clinical trials with PD-1 or PD-L1 inhibitors? If usual PBAC processes were to be followed, when would you expect to make an application for subsidy for these indications?
    - How does your organisation decide which indications to study and which to prioritise for registration or subsidy?

14. Are there effective international models for multi-tumour subsidy that could be applied in Australia within the current regulatory framework?

15. **(For Industry)** What information can you provide regarding established international agreements for multi-tumour subsidy and how could these apply in the Australian regulatory context?

16. Is there anything else you/your organisation would like to add?

[i] www.canceraustralia.gov.au/affected-cancer/what-cancer; accessed 30 April 2018
[ii] Recommended for PBS subsidy in March 2018. Progress to listing requires sponsor and Government agreement
[iii] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/agenda/july-2018-pbac-meeting-agenda
[iv] Department of Health & Ageing; 2009. Review of HTA in Australia
v Ibid;
vi Department of Health, About Health Technology Assessment, http://www.health.gov.au/internet/hta/publishing.nsf/Content/about-1
[vii] Review of HTA outcomes and timelines in Australia, Canada and Europe 2014-2015 (Centre for Innovation in Regulatory Science (CIRS) R&D Briefing 64)
[viii] *National Health Act 1953*, section 101(3)
[ix] Example: 2008: Bevacizumab was granted accelerated approval by the US FDA for the treatment of metastatic breast cancer. However, approval was revoked in 2011 when further follow up showed little benefit and several side effects / toxicities.
[x] http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.9503; https://www.onclive.com/conference-coverage/aacr-2017/fiveyear-survival-rate-an-impressive-16-with-nivolumab-in-advanced-nsclc
[xi] BMJ 2017; 359: j5387; 22 November,2017