Submission Template

Pharmaceutical Benefits Advisory Committee (PBAC)
PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types

Cover sheet

This submission template should be used to provide comments on the Background paper relating to the PBAC consideration of PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types

Contact Details

Company/Organisation represented:	The Australasian College of Dermatologists
Contact name:	Dr Haley Bennett
Phone number:	[redacted]
Email:	haley@dermcoll.edu.au
Date of submission:	
Category of submitting individual/organisation	Are you (select one only) ☐Patient ☐Consumer organisation ☐Pharmaceutical industry ☐Healthcare Provider ☒Professional organisation ☐Researcher ☐Government Body ☐Other (please outline)
Confidentiality and publishing of submissions	Please note - all submissions received will be published on the PBS website at the conclusion of the public submission period, unless otherwise requested. Where submissions indicate commercial-in-confidence or sensitive personal information, this is redacted before publication. Please ensure any commercial –in-confidence or sensitive information is clearly marked.

Submission Instructions

Submissions should be made by **5pm AEST on 29 June 2018**. The PBAC will not consider late submissions.

Submissions should be lodged electronically, preferably in this template, in Microsoft Word or other text based formats, to the email address pbac@health.gov.au

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

General/overall comments

Please note, comments that are beyond the scope of PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types will not be considered

The Australasian College of Dermatologists (ACD) is the sole medical college accredited by the Australian Medical Council for the training and continuing professional development of medical practitioners in the specialty of dermatology. The College is the leading authority in Australia for dermatology, providing information, advocacy and advice to individuals, communities, government and other health stakeholders on dermatological practice in Australia. As the national peak membership organisation, the College represents over 500 specialist dermatologist Fellows (FACD) and 100 trainees across the country.

As specialists in skin cancer, dermatologists are experts in the early detection, diagnosis and treatment of melanoma and non-melanoma skin cancers. An estimated 14,320 new cases of melanoma will be diagnosed in 2018 and, according to recent Australian data, 92% of melanoma diagnoses are at early stage (I and II).[1,2] Thus, dermatologists are essential and appropriate providers of care for a large proportion of patients with melanoma. For patients with metastatic disease, dermatologists play a critical role in their diagnosis and tertiary referral and in many cases an ongoing role in their multidisciplinary care and long-term surveillance.

The College welcomes the invitation to lodge a submission for consideration by the Pharmaceutical Benefits Advisory Committee (PBAC) on the pan-tumour listing of PD-1 and PD-L1 checkpoint inhibitors. This novel class of drugs has had considerable impact on the treatment options available to patients with malignant melanoma, offering improved progression-free and overall survival compared with conventional chemotherapy.[3] This has led to the PBS listing of pembolizuman and nivolumab for patients with unresectable Stage III or Stage IV disease, with other applications under consideration by the PBAC (nivolumab for adjuvant treatment of patients who have undergone resection; combined nivolumab and ipilimumab [CTL4 inhibitor] for unresectable Stage III or Stage IV malignant melanoma). New international studies are investigating checkpoint inhibitors for melanoma treatment in various settings, such as in the neoadjuvant setting, which may provide further evidence supporting a range of indications or eligibility for these agents.[4]

In addition to melanoma, dermatologists are involved in the diagnosis and treatment of other rarer skin cancer types including squamous cell carcinoma of the head and neck (SCCHN) and Merkel cell carcinoma. Despite TGA approval and clinical evidence of efficacy, there is currently no PBS-subsidised access to checkpoint inhibitors for the treatment of these aggressive cancers. In Nov 2017, an application to the PBAC for nivolumab treatment of platinum-based chemotherapy-resistant metastatic SCCHN was unsuccessful.[5] At the time of writing, an application for pembrolizumab for this same patient population is under consideration, as is a newer PDL-1 inhibitor avelumab for the treatment of Merkel cell carcinoma.[6] Treatment options for these patients are already limited and, should these applications be unsuccessful, individuals will continue to carry the burden of unsustainable out-of-pocket costs.

The College supports the PBAC in its consideration of the broader evidence of benefit with checkpoint inhibitors in a range of cancer types and patient populations. Economic evaluation may support health system-wide cost reductions given the efficacy of immunotherapies in a stratified subset of patients.

1. Cancer Australia 2018. Melanoma of the skin statistics. https://melanoma.canceraustralia.gov.au/statistics. Accessed June 2018
2. Cancer Australia 2018. National cancer stage at diagnosis data. https://ncci.canceraustralia.gov.au/features/national-cancer-stage-diagnosis-data. Accessed June 2018
3. Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev. 2018 Feb 6;2:CD011123
4. Clinicaltrials.gov 2018. Neoadjuvant and Adjuvant Checkpoint Blockade in Patients With Clinical Stage III or Oligometastatic Stage IV Melanoma. https://www.clinicaltrials.gov/ct2/show/NCT02519322?term=NCT02519322&rank=1. Accessed June 2018.
5. Pharmaceutical Benefits Scheme. PBAC Public Summary Documents - November 2017. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-11/files/nivolumab-scchn-psd-november-2017.pdf. Accessed June 2018
6. Pharmaceutical Benefits Scheme. Agenda for the July 2018 PBAC Meeting. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/PBAC-meeting-agenda-July-2018-v3.pdf. Accessed June 2018.

Specific responses

Please insert your comments against the consultation questions below.

Question 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?

Multi-tumour listings of PD-1 and PD-L1 checkpoint inhibitors would grant affordable access of these potentially life-saving treatments to patients not currently eligible for PBS subsidy. Using melanoma as an example, there is considerable evidence of checkpoint inhibitor efficacy from clinical trials of patient populations and treatment settings not currently represented on the PBS. Some recent studies include:

Nivolumab

- Patients with resected Stage III or IV melanoma; adjuvant treatment
  - Results showed a 12-month rate of recurrence-free survival for adjuvant nivolumab of 70.5% (95% CI, 66.1 to 74.5)[1]
- Patients with unresectable Stage III or IV melanoma; treatment – naïve
  - Results at 36 months showed median overall survival (OS) of 37.6 months for nivolumab; median OS had not been reached for combination nivolumab + ipilimumab[2]
- Patient with unresectable Stage III or IV melanoma who have progressed after ipilimumab or ipilimumab + BRAF inhibitor
  - Results showed objective response in 38 (31·7%, 95% CI 23·5–40·8) of the first 120 patients in the nivolumab group versus five (10·6%, 3·5–23·1) of 47 patients in chemotherapy group[3]

Pembrolizumab

- Patients with resected Stage III or IV melanoma; adjuvant treatment
  - Results showed significantly longer recurrence-free survival than placebo 75.4% [95% C}, 71.3 to 78.9] vs. 61.0% [95% CI, 56.5 to 65.1][4]

In addition, a consideration of multi-tumour listings would benefit patients with rare cancers where trial data is lacking due to small patient numbers. The aggressive nature of some rare cancers can mean that clinical benefit, while statistically significant in terms of trial outcomes, may be considered too small to justify in economic evaluations. This was evident in the recent failed application of nivolumab for SCCHN, where the PBAC stated that 'economic evaluation of existing trial data may arrive at the uncertainty in the nature and magnitude of its incremental clinical benefit'[5], although trial data showed that overall survival was significantly longer with nivolumab than with standard therapy (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; P=0.01).[6] Merkel cell carcinoma is another good example whereby a flexible approach may be required; with an incidence rate of 1.6/100,000 population in Australia and a median survival of 9.6 months[7], these patients are at a considerable disadvantage compared with higher incidence cancers, where dedicated investment in clinical trials has led to the generation of large and robust clinical datasets. Multi-tumour listings for TGA-approved indications would remove this obstacle and permit affordable access for all patients likely to benefit from checkpoint inhibition.

1. Weber J et al. N Engl J Med. 2017 Nov 9;377(19):1824-1835.
2. Wolchok JD et al. N Engl J Med. 2017 Oct 5;377(14):1345-1356.
3. Weber JS, et al. Lancet Oncol. 2015 Apr;16(4):375-84.
4. Eggermont AMM et al. N Engl J Med. 2018 May 10;378(19):1789-1801.
5. Pharmaceutical Benefits Scheme. PBAC Public Summary Documents - November 2017. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-11/files/nivolumab-scchn-psd-november-2017.pdf. Accessed June 2018
6. Ferris RL et al. N Engl J Med. 2016 Nov 10;375(19):1856-1867.
7. NPS Medicinewise. Avelumab for Merkel cell carcinoma. https://www.nps.org.au/australian-prescriber/articles/avelumab-for-merkel-cell-carcinoma#r1. Accessed June 2018.

Question 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?

A potential disadvantage of the PBAC considering PD-1 and PD-L1 inhibitors for multi-tumour listings could rest with the timing. Given the number of ongoing trials of these agents in a range of indications not currently funded by the PBS, consideration of a pan-tumour listing at this point in time may be premature. Should this be rejected by the PBAC or the Minister, there a risk that subsequent applications to the PBAC for individual indications may be more heavily scrutinised or held against outcomes from this consultation, potentially disadvantaging patients and delaying access.

Question 3

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

Urgent clinical need should be defined as where there are no existing treatment options for metastatic disease that have a known survival benefit; or where PBS eligibility criteria are inflexible and exclude a subset of patients for which there is sufficient clinical trial evidence of benefit.

Question 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?

Optimally, Phase III trials that meet their primary endpoint of overall survival or progression-free survival compared with the accepted standard of care are the gold standard for evidence of efficacy. However earlier phase trials that incorporate survival data into primary or secondary outcome measures should be considered by PBAC as adequate evidence for rarer indications. For example, results from a single-group, open-label Phase II trial was considered sufficient evidence for the TGA approval of avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma. A similar approach by the PBAC should be considered for rarer cancer types, where Phase III trial funding is limited and lengthy recruitment can delay timely evidence generation.

For cancer types for which there is no validated biomarker, it is difficult to predict which patients are likely to respond to treatment. As such, trial data without patient stratification may be impacted as non-responding patients are included in primary datasets. Subgroup analyses however might identify patients who benefit. PBAC should consider evidence from subgroup analyses according to biomarker expression, noting that certain weighting could be given to pre-specified analyses over those which are exploratory, ad hoc or post hoc.

Question 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?

Current evidence suggests that variations in response exist even within a cancer type at the same stage; in metastatic melanoma, more than 50% of patients do not respond to checkpoint inhibitors. Furthermore, a biomarker that has been validated as a good predictor of response in one cancer type may not necessarily be a reliable indicator in another. However given the positive impact of checkpoint inhibition on survival for various cancers, it is imperative that this be balanced against existing therapies, adverse event profiles, quality of life and other endpoints when considering a pan-tumour listing.

Question 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?

Question 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?

Question 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?

In May 2017, the FDA made a landmark decision of granting accelerated approval to pembrolizumab for patients with unresectable or metastatic solid tumours with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) biomarkers. The PBAC should maintain a close watching brief on the outcomes of this decision with respect to patient survival benefit and health system costs.

Question 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.

Yes, this is appropriate. This approach was justifiably used for the PBS listing of nivolumab for the treatment of unresectable Stage III and IV melanoma (cost-minimisation basis with pembrolizumab).

Question 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?

See question 4

Question 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.)

Question 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?

Question 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?

Question 14

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

See question 8

Question 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?

Question 16

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