Options for listing PD-(L)1 checkpoint inhibitors for multiple cancer indications on the PBS

1 Introduction

1.1 In late 2017 the Hon Greg Hunt MP, Minister for Health requested that the Pharmaceutical Benefits Advisory Committee (PBAC) provide advice on options for listing programmed death (ligand)-1 (PD-(L)1) checkpoint inhibitors for the treatment of multiple cancer indications on the Pharmaceutical Benefits Scheme (PBS).

1.2 Specifically, the PBAC was asked to advise the Minister on 1) the current status of PD-(L)1 checkpoint inhibitors for the treatment of cancer; 2) any issues around access to medicines for people with rare cancers, particularly where there are no existing effective therapies; and 3) options that could broaden or lead to faster PBS listing for cancer indications.

1.3 The advice to the Minister from the PBAC was to take into consideration the existing legislative and policy framework for PBAC decision-making that requires PBS listed medicines to be safe, effective and cost-effective compared to alternative treatments. Additionally, any advice was to take into account the role of the Therapeutic Goods Administration (TGA) in approving medicines for marketing in Australia.

1.4 The PBAC elected to publish its initial views on this topic through a discussion paper and to seek input from interested stakeholders ahead of further consideration at its August and November 2018 meetings.

2 Background

2.1 The PBAC discussion paper was published on the PBS website on 25 May 2018 (http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/august-2018-special-meeting/august-2018-pbac-special-meeting-background-paper.pdf) together with an invitation for submissions. The Chair of the PBAC also held discussions with relevant industry working parties, Rare Cancers Australia and the Medical Oncology Group of Australia.

2.2 An environmental scan to determine how other jurisdictions manage the same issue found that neither the United Kingdom's National Institute for Health and Care Excellence (NICE), nor the Canadian Agency for Drugs and Technologies in Health (CADTH) had an explicit, stand-alone process for assessing PD-(L)1 checkpoint inhibitors across multiple cancer types. Belgium, Denmark, Germany, Italy and the Netherlands had introduced systems that were variations on their standard reimbursement processes and that operated in a similar manner to price volume agreements or managed access programs (MAP) in Australia.

2.3 In 2014, the Food and Drug Administration (FDA) in the United States instituted its Breakthrough Therapy pathway to expedite the development and review of medicines that are intended to treat a serious condition and preliminary clinical evidence indicates that the medicine may demonstrate substantial improvement over available therapy on clinically significant endpoint(s)[1]. In May 2017, the FDA granted accelerated approval to pembrolizumab for the treatment of adult and paediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) (a) solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options, or (b) colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (Limitation of Use: The safety and effectiveness of pembrolizumab in paediatric patients with MSI-H central nervous system cancers have not been established).

2.4 In 2018 the TGA introduced the provisional approval pathway which allows sponsors to apply for time-limited provisional registration on the Australian Register of Therapeutic Goods (ARTG). It provides access to certain promising new medicines where it is considered that the benefit of early availability of the medicine potentially outweighs the risk inherent in the fact that additional data are still required.

2.5 At the same time, the TGA introduced a priority approval pathway. The TGA priority approval pathway provides a formal mechanism for faster assessment of vital and life-saving prescription medicines.

3 PBAC Consideration

Stakeholder submissions

3.1 The PBAC acknowledged the considerable input received through the submissions to the meeting and the diverse views put forward by different stakeholders.

3.2 The PBAC noted that twenty eight (28) submissions had been received from a range of stakeholders including nine (9) from industry representatives or representative groups; five (5) from clinical representative groups; four (4) each from consumer representative groups and individual consumers and three (3) each from academic research groups and Health Technology Assessment groups. Twenty-five (25) of the submissions have been published in full, or in part on the PBS website. Copies of all public submissions to the PBAC can be accessed from the PBS website

[1] https://www.fda.gov/ForPatients/Approvals/Fast/ucm405397.htm

3.3 (http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/agenda/august-2018-pbac-special-meeting).

3.4 The key themes emerging from the consumer representative and patient submissions are:

- The PBS processes should not preference specific disease groups in considering new medicines.
- Resources for drug access and subsidy should be allocated in an evidence-based process.
- The whole community needs to be able to trust in the transparency of decision making as supported by the current framework.
- There is a concern that funding of certain diseases / population groups is occurring outside of the objectives of the National Medicines Policy.
- The safety and benefits of medicines should be proven before access is subsidised.
- Clinical trials and other access programs should be separate options for patients, not linked to sponsor applications for PBS subsidy.

3.5 The PBAC noted that other views presented in the broader set of submissions included:

- Sixteen (16) of the submissions explicitly supported an alternative approach for listing PD-(L)1 checkpoint inhibitor immunotherapies for the treatment of multiple cancer indications on the PBS.
- Nineteen (19) submissions were not in favour of the PBAC setting aside one meeting a year for the sole consideration of this class of medicines at the expense of other medicines.
- A common advantage of an alternative approach for multi-tumour listings perceived by respondents was the potential for accelerated/earlier access for patients (particularly for patients with rare cancers).
- A further common advantage cited by pharma industry and research group respondents was the potential efficiencies in workload for some stakeholders, through reducing the need to consider each indication individually.

- Common disadvantages cited across respondents were the likely inequities in access resulting from prioritising a class of medicines at the expense of other medicines, limitations in the predictive ability of PD-L1 or other biomarker expression and the potential for causing harm when allowing use in cancers where there is limited evidence of treatment effect.

- Mixed responses were received in relation to whether it would be appropriate to extrapolate evidence from one tumour type to another, from late to early stage cancer, or from one drug in the class to another, with some respondents supporting this approach and some rejecting it.

3.6 The PBAC noted that a number of submissions also proposed access models for consideration. Those models are discussed in more detail below.

Current status of PD-(L)1 checkpoint inhibitors and timelines to listing

3.7 The PBAC notes that at 1 December 2018, there are two PD-1 checkpoint inhibitors, nivolumab (Opdivo®) and pembrolizumab (Keytruda®) and one PD-L1 checkpoint inhibitor, atezolizumab (Tecentriq®), available on the PBS for a range of indications. A further PD-L1 medicine, avelumab (Bavencio®), was recommended for subsidy at the July 2018 meeting of the PBAC (see Table 1).

Table 1: PBS listing/PBAC recommendation date of PD-(L)1 inhibitors

Tumour Type	Medicine	Date of first PBS listing/recommendation for subsidy (if not listed)
Melanoma	Pembrolizumab (Keytruda®) Nivolumab (Opdivo®)	1 September 2015
Non-Small Cell Lung Cancer	Nivolumab Atezolizumab (Tecentriq®) Pembrolizumab	1 August 2017
Renal Cell Cancer	Nivolumab	1 August 2017
Hodgkin's Lymphoma	Pembrolizumab	1 May 2018
Head and Neck	Nivolumab	1 August 2018
Merkel cell carcinoma	Avelumab (Bavencio®)	Recommended July 2018
Urothelial	Pembrolizumab	Recommended July 2018

3.8 A total of 43,541 pembrolizumab, 45,183 nivolumab and 309 atezolizumab PBS scripts have been supplied through the PBS between the first PD-(L)1 checkpoint inhibitor

listing in September 2015 and June 2018. A rapid increase for nivolumab was observed in August 2017, reflecting the listing of non-small cell lung cancer (NSCLC) and renal cell cancer (RCC) (see Figure 1).

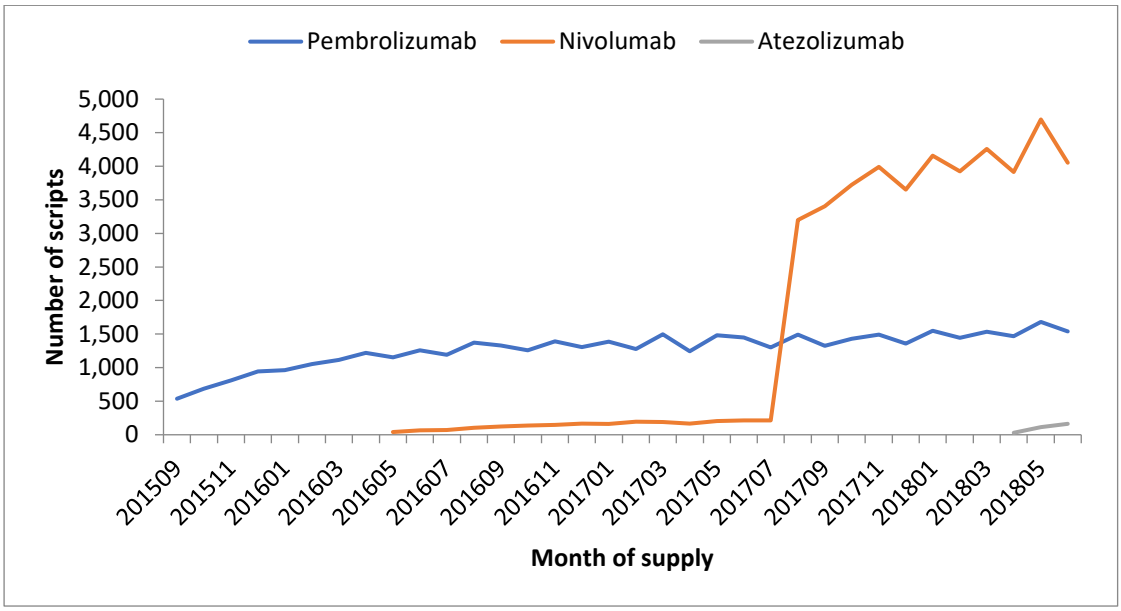

Figure 1: Number of PBS subsidised scripts dispensed for PD-(L)1 inhibitors between September 2015 and June 2018

3.9 The PBAC noted that it had considered 31 subsidy applications for PD-(L)1 checkpoint inhibitors between March 2015 and July 2018. These applications covered seven distinct tumour types and subsidy has been recommended for all seven tumour types. Five submissions for four medicines across three tumour types, one of which is new, were considered at the November 2018 PBAC meeting. Three submissions for three medicines across three tumour types, one of which is new will be considered at the March 2019 meeting. Further information on the applications considered by the PBAC is contained in **Attachment A**.

3.10 The PBAC also noted that new therapies involving immuno-oncology medicines including PD-(L)1 checkpoint inhibitors and other classes of medicines are being rapidly developed and that a significant number of new PBAC submissions is anticipated over the next 18 to 24 months.

3.11 The PBAC noted that the majority of responses acknowledged that it was appropriate to both require the provision of, and assessment of, the evidence–base for a medicine for PBS listing and reimbursement.

3.12 However, the PBAC noted the perception amongst stakeholders that the time to PBS listed access for PD-(L)1 checkpoint inhibitor medicines is too long.

3.13 The PBAC noted that the time from registration to reimbursement is influenced by a range of factors including:

- the date a submission is first made to the TGA and the PBAC;
- the number and timing of re-submissions required to achieve a positive PBAC recommendation; and
- the time taken to finalise pricing, risk-sharing arrangements and other matters following a positive PBAC recommendation.

3.14 The PBAC noted that the timing of submissions for registration and/or reimbursement in Australia was frequently later than in overseas jurisdictions. Examples are provided in Table 2 (see also **Attachment A**).

Table 2 Comparison between timing of submissions for registration and/or reimbursement in Australia and overseas jurisdictions

Medicine	Indication	Date FDA approved	Date EMEA Approved	Date TGA evaluation commenced	Date first PBAC consideration
Pembrolizumab	Treatment of patients with advanced microsatellite instability-high (MSI-H), including mismatch repair deficient (dMMR) cancer who have received prior therapy	23 May 2017	Not approved	[redacted]	March 2019 (colorectal cancer only)
Atezolizumab	Locally advanced or metastatic NSCLC with progression on or after prior chemotherapy.	18 October 2016	20 July 2017	31 July 2016	November 2017
Nivolumab	Advanced clear RCC after prior anti-angiogenic therapy	23 November 2015	25 February 2016	[redacted]	July 2016

3.15 The PBAC noted the time from registration to reimbursement for PD-(L)1 checkpoint inhibitors in Australia ranged from 111 to 1,055[2] days with an average of 390 days and a median of 320 days (see also **Attachment A**). This is consistent with the average time for PBS listing of other medicines and the subsidy consideration timelines of international bodies.

There are many examples of very rapid listing where drugs have high unmet clinical need, in these circumstances the listing has often occurred significantly in advance of reimbursement in other countries. For example, the TGA registration of pembrolizumab for melanoma was approved on 16 April 2015 and PBS subsidy

[2] Assuming the July 2018 positive PBAC recommendation for nivolumab in combination with ipilimumab in melanoma leads to a 1 December 2018 PBS listing.

commenced on 1 September 2015, some four-and-a-half months later.

In contrast, the TGA registration of nivolumab in combination with ipilimumab for the treatment of melanoma was initially approved in January 2016 and the PBAC first considered a subsidy application for that use in November 2015. However, two further PBAC applications (March 2017 and July 2018) were required before subsidy could be recommended. As a result 1055 days will have elapsed since registration when this listing proceeds on 1 December 2018. Notably, the majority of that time period is a result of the time taken by the sponsor to re-submit to PBAC. If the sponsor had resubmitted sooner, a July 2016 (2nd submission) or March 2017 (3rd submission) PBAC recommendation may have been achieved.

3.16 The PBAC noted that regulators and reimbursement bodies faced a tension between achieving faster access to medicines in the face of high clinical need while meeting their core obligations to ensure safety (in the case of the TGA) and cost-effectiveness (in the case of the PBAC). The PBAC noted that many of the access issues identified during consultation were outside of its legislated framework and scope such as indications for which a medicine was not registered or funding of medicines for clinical trial access.

3.17 The PBAC considered other policy ideas and international responses to this issue such as the UK Cancer Drug Fund and noted learnings from this, as well as learnings from previous approaches used by the PBAC and government to resolve uncertainty around PBS listing, such as Managed Access Programs.

3.18 The PBAC further noted the UK Cancer Drug Fund has been substantially redesigned recently and now operates similarly to the Australian Managed Access Program arrangements, albeit within an overall fixed funding cap and with clearly defined review mechanisms and timeframes for establishing ongoing subsidy arrangements (price, indications for use etc.) where the longer term evidence supports this. The UK Cancer Drug Fund also does not include processes for ceasing subsidy for medicines where the longer term evidence does not support ongoing subsidy.

3.19 The PBAC noted that an arrangement of this type could potentially be used to provide access to medicines considered by the PBAC to meet a high and unmet need, while a subsidy application is being considered.

3.20 The PBAC further noted that, although some other international bodies had made some modifications to their processes, most had not significantly adjusted their standard processes to facilitate subsidy of this class of medicines.

3.21 The PBAC did not agree that the potential to reduce the workload for applicants and the Committee is, of itself, a sufficient reason to change process, particularly in the

context of a treatment which has not been shown to be beneficial in all cancer types and which has the potential to cause harm.

3.22 The PBAC noted that the parallel consideration of TGA applications and PBAC submissions had already led to overall reductions in the time between TGA approval and PBS listing. The PBAC acknowledged that the TGA priority and provisional approval pathways may provide additional opportunities to ensure timely access for consumers and reiterated its commitment to working with all stakeholders to ensure the opportunities afforded by these new regulatory processes are utilised.

3.23 The PBAC noted there are a number of parallel initiatives related to the Strategic Agreement with Medicines Australia that are seeking to improve the efficiency, transparency and timeliness of PBS listing processes and which should further improve access to new medicines and/or indications.

3.24 The PBAC considered that not all respondents were well informed about Government registration and reimbursement processes for medicines and that ongoing communication was required to provide stakeholders with accurate information.

3.25 The PBAC also considered that greater transparency around conditions of reimbursement, including price negotiation issues and pricing agreements, may also assist in managing the perception of delays to access. The PBAC noted that with the agreement and cooperation of sponsors it would be possible to greatly increase transparency for consumers and the public more generally.

Access to PD-(L)1 checkpoint inhibitors for diseases with limited clinical evidence (including rare cancers)

3.26 The PBAC acknowledged respondent concerns around equity of access for diseases where the evidence is limited, and some views that the current PBAC process does not work for these conditions.

3.27 The PBAC noted that it had recommended medicines for PBS listing based on a range of trial and evidence types, and, although there is a preference for, there is not a requirement for, Phase III randomised controlled trial evidence to support applications for PBS listing of medicines. The preference for Phase III studies is because they have greater reliability than other types of studies.

3.28 The PBAC noted it has recommended PD-(L)1 checkpoint inhibitors for three rare cancers; Merkel cell carcinoma, squamous cell carcinoma of the head and neck and classical Hodgkin lymphoma and confirmed it would continue to review clinical evidence with appropriate consideration of unmet medical need.

3.29 The PBAC considered that the majority of cases with no access to PBS subsidised treatment in the longer term are for medicine-indication pairs that are not TGA registered. The PBAC noted many cancers for which there is limited evidence of the benefits of treatment with particular medicines, including rare cancers, tended to fall into this category.

3.30 The PBAC considered that the PBS is generally not an appropriate funding source for medicine-indication pairs not registered by the TGA. The issues that arise from such an approach include: lack of conformity with the requirements of the *National Health Act 1953*; precedents for decision making; and the potential for significant expenditure without reasonable return. Additionally, the PBAC noted the additional risks for all stakeholders when medicines are prescribed off-label (i.e. outside TGA-approved indications).

3.31 The PBAC indicated it would continue to encourage sponsors, clinical expert groups and other stakeholders to make registration and funding submissions to address areas of unmet clinical need wherever possible. However the PBAC also noted that such an approach was usually only possible where there is sufficient evidence available to support such submissions.

3.32 The PBAC noted that other mechanisms exist for patients to access medicines without PBS subsidy, including through clinical trials that are sponsor or government funded, through compassionate access programs and through public hospital based arrangements.

Proposed options to broaden PBS listings or decrease time to access

3.33 The PBAC noted the revised medicine access models proposed in a number of stakeholder submissions which included:

- Use of standard pre-determined pricing structures such as tiers or common prices across multiple indications, with prices determined based on surrogate outcomes, established scores of clinical value or by using anchor, or first indication, prices for second and subsequent indications.
- Modified pay-for-performance and managed access scheme structures for example, for rare cancers.
- Abbreviated HTA processes.
- Early listing with development of post market clinical data.
- Boosting clinical trial participation, with a focus on identifying where there is a clinical need and gaps in the evidence base.

3.34 The PBAC noted that in the models presented in the industry stakeholder submissions, no consistent or significant improvements in time to access were apparent, and that the submissions provided limited justification for a shift from current process. These submissions were also focused on indications where there was an established TGA registration in place, thereby excluding potential benefits for less common or rare cancers where registration did not exist or was not likely.

3.35 The PBAC also considered that all presented models shifted the workload to earlier and/or later in the PBS listing process rather than eliminating or reducing workload. If anything, the proposed models were likely to increase the administrative burden on clinicians and payers. Additionally, they would likely require significant up-front price reductions or lower initial list prices to address the high level of uncertainty of cost-effectiveness. Such lower prices may not be acceptable to sponsors given international market arrangements.

3.36 The PBAC reiterated its concern that the clinical results for PD-(L)1 checkpoint inhibitors have been variable to date. 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 tumour mutational burden (TMB) may be useful in some cancers, but biomarker trial approaches, and the results are variable, which leads to uncertainty in decision-making where biomarkers are used. Research is still being undertaken to identify and validate accurate biomarkers.

3.37 This view is supported by an analysis of the previous PBAC medicine submissions for PD-(L)1 checkpoint inhibitors which found there was considerable heterogeneity in the clinical outcomes observed across cancer indications; between lines of therapy within a cancer indication for a specific medicine; and between medicines of the same class within a cancer indication, within the same line of therapy. Based on this analysis, it did not presently appear possible that an adequate single reference model could be developed that would allow for consideration of different tumour types, or biomarker defined subgroups, medicines or lines of therapy.

3.38 The PBAC considered that in the circumstance of limited evidence, or highly extrapolated evidence, there was a significant risk of causing harm either directly (forgoing effective current standard treatments, adverse events) or intangibly (false hope, not resolving patient needs, inadequate provision of palliative care).

3.39 The PBAC considered that in general, extrapolation between tumour types, lines of therapy and PD-(L)1 checkpoint inhibitors was currently not reasonable and noted the limited support for various types of extrapolation in the stakeholder submissions.

3.40 However, the PBAC considered this is not true for all uses of these medicines. For example, substantial evidence and experience is available for PD-(L)1 checkpoint

inhibitors in lung cancer and consideration of a broader lung cancer listing across all PD-(L)1 checkpoint inhibitors may be warranted.

3.41 The PBAC noted that, contrary to the assertion of Medicines Australia (and others), that applications for PBS subsidy could only be made for an indication/single tumour type at a time, a biomarker/mutation multi-tumour submission is possible using current processes and Managed Access Program arrangements. Applicants seeking a broad listing for a tumour group based on a biological marker or other common feature can make applications for subsidy now providing they have some evidence to show effectiveness for that group of cancers. There are no specific barriers to such an application. However, no sponsor has availed itself of this opportunity to date.

3.42 The PBAC supports the use of different types of evidence providing that the evidence allows the PBAC to make a judgement about relative value. Within the range of clinical study types available, some provide better and some worse bases for decision makers. For example, basket trials test one type of targeted therapy on several tumour types. However, these trials do not include controls and are almost entirely reliant on response rates as the signal of effect (which is a poor predictor of benefit for many tumours). So these studies are at best 'signal finding' trials and, while useful innovations in clinical research, may not be that useful for decision making for reimbursement. On the other hand, umbrella studies allow for testing multiple targeted treatments for one or more tumour types and incorporate randomisation in the sub-studies. Platform trials have advantages over both these other two approaches but they also have limitations including that they take a long time and involve Bayesian methodology.

3.43 The PBAC noted that other types of evidence can also be used in reimbursement submissions, including evidence from early stage clinical trials and real-world evidence. Of critical importance for the PBAC is the suitability of the evidence base for informing an assessment of the comparative benefits and harms of the proposed new treatment with currently available treatments.

3.44 The PBAC also considered it pertinent that there are very few current examples of biomarkers reliably predicting response across tumour types. For example, although BRAF mutations usefully predict response to BRAF inhibitors in melanoma, BRAF inhibitors are not active in BRAF-mutant colorectal cancer; HER2 usefully predicts response to trastuzumab in breast cancer and is a more modest predictor of response in gastric cancer, but has not otherwise proven to be a useful predictor for response. [redacted]

3.45 Overall, the PBAC considered it may be appropriate for further guidance to be developed on approaches to multi-tumour submissions based on a biomarker, mutation or other common feature.

3.46 The PBAC noted that Medicines Australia and MSD's proposals comprised three separate elements.

- A streamlined submission process for second and subsequent PBS indications ("follow on indications") for which randomised clinical trials are being pursued, using a pre-agreed per patient cost (anchor price) and patient numbers to enable early listing, with verification of cost effectiveness and price adjustment (upwards or downwards, but not retrospectively) after four years of listing;

- A pay-for-performance type pathway for rare diseases with limited data but biological plausibility for response; and

- A price volume arrangement covering 3 years, to complement the other two elements, manage the overall budget, and allow for sponsors to offer discounts.

3.47 The PBAC acknowledged the potential utility of such a broad approach, but had a number of concerns with how these proposals could be used to improve time to access including that: the basis for agreement of the criteria for entry (clinical benefit) and listing parameters (anchor price, patient numbers, retreatment options price adjustment mechanisms and rebate arrangements) and mechanisms for ceasing subsidy (managed exit) were not clear. Considerable 'up-front' PBAC and Department time and effort would be needed to establish these parameters. It is also unclear how use in unregistered indications might be feasible or how the proposal aligns with TGA processes for evaluation and decision-making.

3.48 The PBAC was also concerned that, despite the authors contrary assertions, these arrangements might not be consistent with the *National Health Act 1953* because they may result in a higher price than is cost effective being paid for a long period without avenues for recovery of overpayments. The alternative, where the agreed price ensured cost effectiveness across all indications, was considered unlikely to be acceptable to companies. Additionally, these proposals require mechanisms to collect data, but provide scant detail on the suitability or feasibility of current Australian systems for this activity, or how it would be funded.

3.49 The PBAC noted that the Bristol Myers Squibb Australia (BMSA) proposal to use a surrogate marker of response as a means of initial price setting, whilst promising, was based on an analysis of a very limited number of subsidy submissions. The PBAC further noted that the particular surrogate nominated by BMSA did not consistently

correlate with improvements in patient important outcomes such a progression-free and overall survival in other cancer types.

3.50 BMSA's submission noted [redacted]

3.51 The PBAC noted that the various activities already underway to expedite TGA registration for medicines for conditions with a high and unmet clinical need and to improve the efficiency and transparency of PBS listing processes may limit the opportunities for further expediting the assessment process without reducing the rigour of health technology assessment applied. However the PBAC reiterated its commitment to continuous process improvement.

4 Options for consideration by the Minister.

4.1 In providing these options to the Minister for consideration the PBAC notes that:

- The PBAC is required by the *National Health Act 1953* to consider the comparative effectiveness, safety and costs of new medicines (including cost effectiveness and financial affordability) in making recommendations for listing. The objective of greater efficiency of process cannot override these requirements.

- It is important to consider the precedent that a recommendation about any medicine or class of medicines has for broader PBAC processes and for subsequent submissions for other medicines for the treatment of the same indications.

- Its preferred position is not to implicitly or explicitly endorse an approach which preferences recommendations for medicines (or a particular class of medicines) for one disease or sub-set of diseases over other equally devastating diseases.

- Its preferred position is to have as few as possible special access arrangements for specific classes of medicines or conditions.

- It considers any change should not devalue the current PBS system or undermine the importance of evidence generation.

4.2 The PBAC also notes that:

- Broader PBS listings usually come with increased uncertainty on costeffectiveness (value for money) and greater financial risk for government.

- There continue to be areas of high and unmet clinical need including for treatments for less common or rare conditions.

- At the current prices for PD-(L)1 checkpoint inhibitors, a broad PBS listing would be associated with a very high total cost with potential opportunity costs for other diseases.

- Applicants seeking a broad PBS subsidy listing for a tumour group based on a biological marker or other disease feature can make these applications, providing there is some evidence to show effectiveness for the group of cancers.

- Broader listings are more possible when prices are lower as expansion of the patient population impacts on financial affordability. For example, the PBAC has made recommendations for broader listings of medicines whose prices have fallen due to brand competition and where clinical practice has led to wider use, even though the evidence may remain weak for effectiveness for some indications.

- Implementing broader listings is often constrained by TGA-registered indications and the significant impediments to changing registration conditions.

- The Department of Health and sponsors can already negotiate a simplified pricing arrangement (for example by pre-agreeing price or risk share parameters) to achieve faster listings subsequent to positive PBAC listing recommendations.

- The arguments presented for supporting a multi-tumour approach for PD-(L)1 checkpoint inhibitors could equally apply to other medicines in cancer and other medicines for non-cancer conditions where there is a common underlying mechanism of disease.

4.3 With regard to PD-L(1) checkpoint inhibitors and pan-tumour listings the PBAC recommends the Minister request additional advice on:

- Options for a broad PBS subsidy listing for PD-(L)1 checkpoint inhibitors for lung cancer, as substantial evidence and experience is now available for these medicines in this setting.

- Options for a standardised tiered pricing arrangement for PD-(L)1 inhibitors that would apply once the PBAC has recommended subsidy for a particular use and that would account for issues beyond PBAC's scope including economies of scale and affordability considerations.

4.4 With regard to more general issues raised, the PBAC recommends the Minister request additional advice on:

- The development of an Appendix to the Guidelines for Submissions to the PBAC that provides information on possible approaches to multi-indication submissions.

- Clarification of the status of conditional funding arrangements that would complement the TGA provisional registration pathway. These would utilise the established Managed Access Program arrangements and establish transparent, robust and enforceable criteria for reviewing existing funding arrangements for medicines and for managing exit from subsidy. The PBAC acknowledged that the introduction of such arrangements would require legislative change.

- Options for eliminating or reducing the barriers to TGA registration for rare conditions – particularly where the medicine is registered for a range of other conditions, the safety profile of the drug is well known and there is a high unmet clinical need. This is not limited to cancer medicines, but encompasses all medicines, and both existing and new medicines.

- Options for supporting subsidy of medicines outside the PBS for diseases where there is a high and unmet need and where the evidence base is limited. The PBAC's preferred approach is that such access should be within the context of a clinical trial. The PBAC noted the Government's commitment to expanding clinical trial capability in Australia especially in the area of rare diseases and cancers providing opportunities for generating / collecting evidence in these rare condition populations.

- Options for providing subsidised access to medicines considered by the PBAC to meet a high and unmet need, while an application is under consideration.

The PBAC considered that any such scheme would need a tight definition of high and unmet need and defined parameters to limit the period of special funding, as well as other potential measures (e.g. risk share arrangements) to mitigate the risks inherent in such an approach. The PBAC acknowledged that the introduction of such arrangements would require legislative change.

Attachment:

A. List of PD-(L)1 checkpoint inhibitor applications to PBAC between 2015 and July 2018, inclusive.